Pediatrics

VOLUME 10 AUGUST 1952 NUMBER 2

ORIGINAL ARTICLES

GROWTH OF THIOCYANATE SPACE IN INFANCY AND CHILDHOOD

By ROBERT S. ELY, M.D.,* AND WATARU W. SUTOW, M.D.
Salt Lake City

KNOWLEDGE of the changes in the size of the various water compartments during the growth period from birth to maturity both in man and animals is meager. There is some information as to the growth of plasma volume in children.[1-10] However, there are only a few observations referable to total body water[11,12] or extracellular water;[2,11,13-15] and there is a paucity of information concerning the nature and rapidity of alterations in these compartments with growth. Evidence does exist from postmortem dessication studies[16] and in vivo studies that both total body water[12,16] and extracellular water[2,13] decrease with age, this decrease in either case being most rapid during infancy.

The investigations here reported were done to determine the relationship of thiocyanate (SCN) space to age and to delineate any changes in this space which may occur with age. The measurement of SCN-space is employed as a means of approximately determining the volume of that compartment of body water denoted as "extracellular water" and therefore delineating the relationships which may exist between "extracellular water" and age. Substances such as inulin have volumes of distribution that probably more nearly represent a true extracellular compartment. However, the measurement of SCN-space was used because of the simplicity of its technic, and because determination of changes in compartment size rather than of absolute values was the principal objective.

METHODS

The subjects used were elective surgical patients or infants and children who had recovered from acute illnesses. They were clinically in a good state of hydration, with Hgb, hematocrit and RBC values consistent with their ages. All observations were made after a fasting period of 8 to 10 hr.

From the Department of Pediatrics, Stanford University School of Medicine, San Francisco, and the Department of Pediatrics, University of Utah College of Medicine, Salt Lake City.

Supported by Grant-in-Aid from the John and Mary R. Markle Foundation.

(Received for publication June 17, 1951.)

* Present address: Department of Pediatrics, University of Utah College of Medicine, Salt Lake City.

TABLE 1

DATA ON SUBJECTS STUDIED, INCLUDING SURFACE AREA (S.A.), AGE, WEIGHT (kg.), HEIGHT (cm.), SCN-SPACE, PLASMA VOLUME (P.V.) AND BLOOD VOLUME (B.V.) (liters)

Case	S.A.	Age Yr.	Wt.	Ht.	"SCN-Space"	PV	BV
106	0.16	0.15	2.4	44.5	1.112	0.128	0.172
136	0.18	8 days	2.8	47.0	1.000	0.144	0.285
152	0.21	0.25	3.4	51.0	1.610	0.184	0.246
131	0.22	0.30	4.0	49.0	1.733	0.266	0.464
100	0.23	0.37	4.4	50.0	1.745		
34	0.24	0.17	4.1	55.0	1.230		
112	0.26	6 wk.	4.9	55.5	1.864		
23	0.27	1 mo.	5.1	57.0	2.070		
58	0.24	1 mo.	4.1	55.0	1.610		
146	0.30	0.25	5.4	63.0	2.106	0.331	0.517
128	0.31	0.25	6.7	58.0	2.080	0.213	0.358
151	0.32	0.50	6.4	64.0	2.296	0.290	0.425
102	0.33	0.75	7.1	66.0	2.553	0.344	0.595
114	0.34	0.67	7.0	65.0	2.108	0.309	0.585
35	0.34	0.54	7.4	64.0	2.370		
74	0.35	0.59	7.6	64.0	2.000		
21	0.35	0.46	6.2	60.5	2.050		
103	0.36	0.96	7.3	70.0	2.798	0.354	0.578
170	0.37	1.25	7.3	72.0	2.550	0.326	0.518
164	0.38	0.75	8.7	67.0	2.950	0.321	0.506
5	0.41	1.25	9.1	72.0	3.290		
162	0.41	1.00	9.4	71.0	2.975	0.383	0.604
59	0.41	1.25	9.1	73.0	2.610		
119	0.41	1.50	9.1	73.0	2.975	0.451	0.758
123	0.42	0.90	10.2	71.0	3.015	0.593	0.954
169	0.43	1.50	9.4	76.0	3.030	0.355	0.577
176	0.44	1.50	10.1	76.0	3.358	0.426	0.711
84	0.44	1.00	9.1	81.0	3.480		
57	0.44	1.08	10.4	74.0	3.750		
138	0.44	1.30	10.0	77.0	3.475	0.493	0.815
165	0.44	1.50	10.2	76.0	3.488	0.418	0.692
7	0.46	1.50	10.8	76.0	3.450		
135	0.46	1.20	10.5	79.0	4.045	0.604	0.948
163	0.47	1.20	12.7	72.0	3.695	0.363	0.588
168	0.47	1.50	10.5	80.0	3.050	0.381	0.628
14	0.48	1.50	10.7	84.0	3.600		
145	0.50	1.50	12.5	79.0	3.724	0.604	1.016
132	0.50	2.50	10.9	86.5	4.420	0.918	1.530
141	0.50	2.30	11.4	83.5	3.570	0.556	0.849
8	0.52	1.17	14.7	75.0	3.450		
13	0.53	1.50	12.7	86.0	4.020		
15	0.53	2.00	12.7	86.0	3.960	0.716	1.195
117	0.53	1.67	12.7	85.0	3.675		
37	0.53	1.67	12.5	86.0	4.200		
115	0.53	2.60	12.5	85.6	3.656	0.665	1.093
147	0.54	2.10	13.2	86.5	3.935	0.583	1.070
49	0.54	3.00	13.2	85.0	4.900		
111	0.55	3.00	11.8	92.7	3.088	0.495	1.030
118	0.55	2.40	12.5	91.5	3.520		
6	0.56	2.58	12.7	90.0	4.280		
122	0.56	2.10	14.1	86.0	4.335	0.743	1.233
129	0.59	5.30	13.4	96.0	3.680	0.493	0.888
171	0.59	4.70	12.7	98.0	3.545	0.603	0.966
125	0.61	4.40	14.1	97.0	4.380	0.653	1.150

TABLE 1—(*continued*)

Case	S.A.	Age Yr.	Wt.	Ht.	"SCN-Space"	PV	BV
94	0.63	4.5	13.9	103	3.900	0.830	1.414
109	0.64	4.4	15.0	101	4.415	0.855	1.455
116	0.64	4.3	15.0	99	4.100		
153	0.64	5.5	13.2	104	3.790	0.602	0.992
12	0.65	3.58	16.3	96.5	4.500		
159	0.66	4.0	15.6	102	4.750	0.712	1.154
127	0.66	5.6	15.0	104	4.735	0.918	1.541
39	0.71	4.58	19.5	104	5.400		
2	0.72	4.0	18.6	104	6.250		
142	0.73	6.8	18.2	107	5.950		
120	0.73	5.0	18.6	107	5.625	0.907	1.608
104	0.74	4.7	18.4	109	6.580	0.792	1.391
121	0.71	6.5	15.9	118	5.280	0.960	1.654
143	0.74	6.9	18.6	107	5.130	0.990	1.672
3	0.75	7.0	18.1	107	5.882		
43	0.75	8.7	18.6	112	6.080		
173	0.77	5.7	19.1	111	5.190	0.654	0.997
150	0.78	6.1	17.5	120	6.790	0.903	1.553
110	0.79	5.7	18.4	118	5.025	0.904	1.640
130	0.79	8.0	20.0	113	5.840	0.842	1.406
157	0.79	5.1	18.8	118	5.240	0.735	1.289
69	0.84	5.9	21.1	119	6.300		
108	0.88	7.5	22.7	121	6.450	1.284	2.325
124	0.93	7.3	23.6	128	6.670	1.160	2.150
17	0.96	7.0	26.0	128	5.770		
18	0.96	8.7	25.4	130	8.950		
38	0.96	10.0	25.0	130	8.600		
68	0.97	11.0	31.7	116	8.261		
77	0.98	8.5	25.9	131	7.300		
40	1.03	10.8	27.3	135	8.700		
42	1.04	10.5	27.7	136	7.300		
56	1.07	10.7	29.5	135	10.300		
31	1.08	10.0	29.1	137	7.800		
70	1.08	12.0	30.0	136	8.800		
32	1.12	12.0	27.2	148	7.900		
82	1.12	10.0	31.0	142	6.500		
44	1.13	10.3	32.2	140	9.680		
48	1.15	12.8	33.6	141	10.900		
85	1.16	11.0	31.8	144	7.400		
41	1.17	10.5	37.7	137	11.150		
26	1.18	12.0	32.7	146	10.500		
63	1.21	14.0	34.5	146	11.110		
29	1.32	12.3	38.2	154	10.300		
55	1.32	14.2	41.0	149	7.200		
36	1.40	11.8	42.2	157	13.800		
45	1.41	15.1	47.7	152	13.200		
148	1.41	15.9	45.5	156	12.070	1.715	2.975
47	1.42	15.3	43.1	159	12.200		
28	1.44	15.3	42.3	162	12.800		
30	1.52	15.8	50.5	161	10.900		
60	1.56	15.0	49.1	167	15.000		
25	1.60	15.5	51.8	168	14.110		
54	1.60	15.0	57.0	162	19.300		
75	1.64	13.8	56.3	167	14.400		

for infants under 18 mo. of age and of about 15 hr. for older children. T-1824 (Evan's Blue Dye) was used to measure plasma volume and sodium thiocyanate (NaSCN) to determine SCN-space. These materials were weighed together[17] and injected in amounts of 0.5 mg./kg. and 20 mg./kg., respectively. Syringe was then rinsed 2 to 3 times with blood. Blood samples were drawn at 10 min. after injection for dye determinations and at 60 min. for SCN-determinations. All tests were carried out in the the morning. Hematocrit values were obtained after centrifuging at 3000 rpm for 30 min.; dye samples were run immediately.

Blood volume was calculated from the hematocrit and the value for plasma volume obtained by dye method according to the following formula:

$$B\,V = \frac{P\,V}{(100 - \text{Hematocrit})}$$

No correction was made for amount of plasma trapped between centrifuged RBC. "Interstitial space" corresponds to the difference between SCN-space ("extracellular volume") and plasma volume[18, 19] and may be calculated from data on table 1. Inasmuch as SCN-ion enters into the red cell some investigators have used the following formula for "interstitial space": "extracellular space"—.70 blood volume. This correction was not applied here since SCN-space values are only approximations of "extracellular space" and because relative rather than absolute values were of primary interest. It is to be emphasized that "interstitial space" represents only an approximation of that compartment's true value.

Thiocyanate was measured with photoelectric colorimeter by a modification of Barker's method.[20] A single sample at 60 min. was obtained for this determination; slope interpolation and renal excretion measurements were not made. The dye, T-1824, was measured by a modification* of Morris' chromatographic method.[21] A 10 min. sample was obtained, again without slope interpolation. Chromatographic method involves adjusting the pH of serum to 10, adsorbing upon an Al_2O_3-MgO column, washing out serum components such as proteins and lipids and then eluting the dye with HCl-alcohol. This method is considered superior to direct dye-plasma readings because with this method 1.0 cc. serum is sufficient for accurate determinations with an ordinary photoelectric colorimeter and because interfering factors such as lipemia, turbidity and hemolysis are considerably diminished.

Results

Data concerning SCN-space are presented on 108 subjects, and concerning plasma and blood volumes on 50 subjects. The age, height, weight and surface areas (surface area obtained from the formula of DuBois and DuBois) of these are recorded (table 1). The ages range from a few days to 16 years. Most of the subjects were less than 2 years of age. The interrelationships of these values are presented in charts 1 to 3. Chart 1 shows the changes of SCN-space with age, height, weight and surface area. The curves relating SCN-space to weight and to surface area approximate straight lines. The curve relating SCN-space to height, however, follows a curvilinear slope which rises slightly. The curve relating SCN-space to age follows, in its early part, a curvilinear course but approaches a straight line after the age of 2 years.

Thiocyanate space as per cent of body weight related to age is shown in chart 2. A definite decrease is seen from birth to about 2 years of age with a gradual downward trend thereafter. This decrease is most pronounced in the first 12 months, the average value for 14 subjects in the first six months of life being 39% of the body weight and for nine subjects in the 6 to 12 month age period being 33%. After the first year the decrease is fairly slow. Plotting the SCN-space as per cent of body weight against surface area, height and weight produces much the same curvilinear relationships.

---

* Modified by Drs. Greenberg and Hecht, Department of Internal Medicine, University of Utah College of Medicine.

Chart 3 shows the changes in blood volume related to age, height, weight and surface area. The relationship of blood volume to age is represented by a curve much like that for SCN-space, curvilinear in its early part but later approaching a straight line. The curve relating blood volume to height appears to approach a straight line. The ratio of the volume of blood to either weight or surface area appears to increase with increasing weight or surface area. When blood volume as per cent of body weight is plotted against age no significant trend is shown.

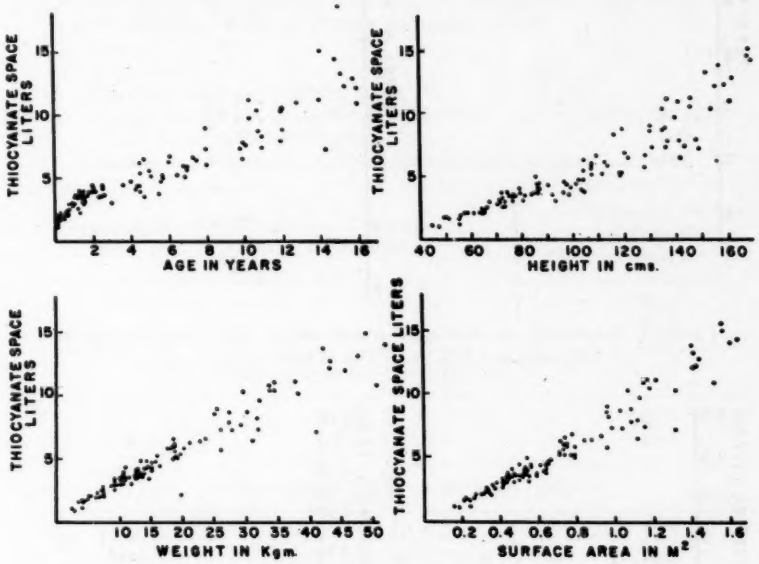


CHART 1. Relationship of SCN-space in liters to age, height, weight and S.A.

"Interstitial space" exhibits much the same relationship as SCN-space, with but one exception: blood volume or SCN-space/unit of surface area increases with either age or increasing surface area; however, "interstitial space"/unit of surface area decreases with either age or increasing surface area.

The significance of the changes with increasing age in SCN-space and "interstitial space," as per cent of body weight, is shown in tables 2A and 2B. Statistical comparison was made by calculating T-values of the difference-means. From table 2A it is seen that the decrease in SCN-space as per cent of body weight from age group 0 to 6 months to age group 7 to 12 months is highly significant, P being only 0.5%. The difference between age groups 1 to 2 years and 3 to 5 years is of only probable significance as not enough cases were present in the latter group to permit strict analysis: P = 5 — 10%. In the 5 to 15 year age group as compared to the 1 to 4 year age group the decrease becomes highly significant, as P is only 0.5%.

"Interstitial space" as per cent of body weight might well show changes even more significant than does SCN-space, were there more values for the former. The differences which exist between the age groups 0 to 6 months and 7 to 12 months, containing only 8 and 6 subjects, respectively, have a T-value of 2.2 and a chance probability of only 2.5%.

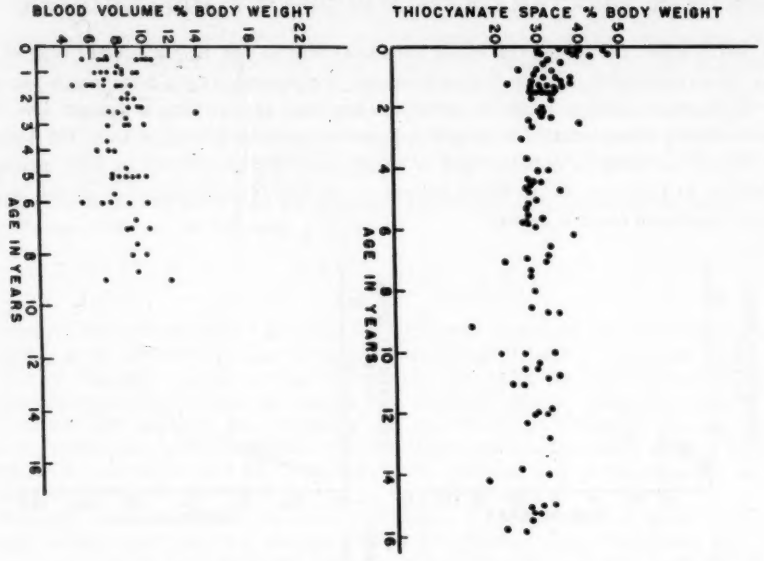


CHART 2. Relationship of SCN-space as per cent of body weight to age, and relationship of B.V. as per cent of body weight to age.

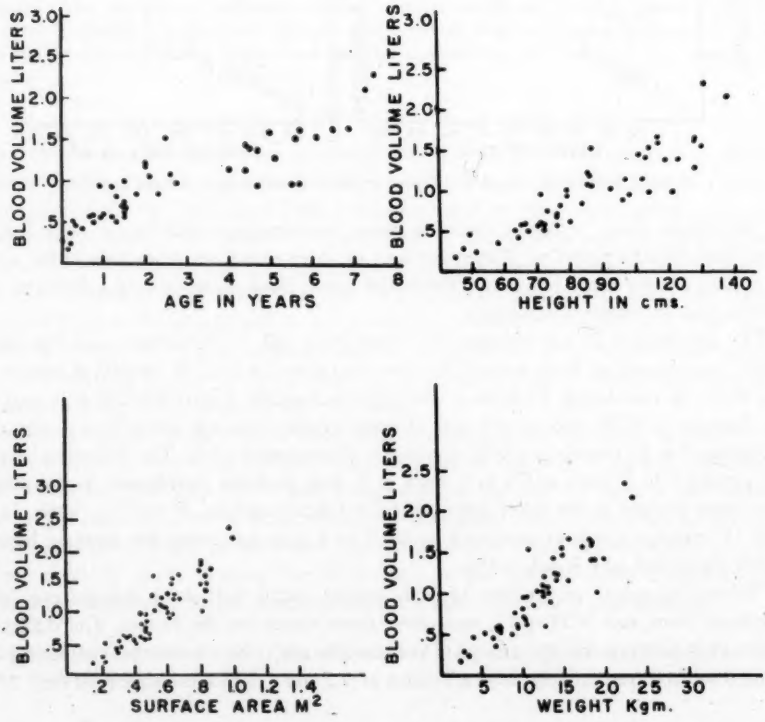


CHART 3. Relationship of B.V. in liters to age, height, S.A. and weight.

TABLE 2A

THIOCYANATE SPACE AS PER CENT OF BODY WEIGHT. DIFFERENCE-MEAN VALUES FOR VARIOUS AGE GROUPS. T-VALUES WERE CALCULATED USING EQUATION:

$$T = \frac{\bar{X}_2 - \bar{X}_1}{S} \sqrt{\frac{(N_1)(N_2)}{N_1 + N_2}}$$

T is variable expressing relation of deviations from mean and standard deviation, with reliability as indicated by degrees of freedom (N−1)
$\bar{X}$ = Mean
N = Number group
S = Standard deviation of difference-means
P—probability prediction, i.e., probability chance alone could account for result, is obtained from tables for "T" values.
(Fisher and Yates, Statistical Tables, Edinburgh, Oliver & Boyd, Ltd., 1949)

Age of Subjects (Yr.)	No. of Subjects	SCN-space as Per Cent of Body Wt. (mean)
0–0.5	14	39.3
0.6–1.0	9	32.9
Difference-mean 6.4 (T=2.79; P=0.5%)		
1–2	27	31.9
3–5	11	29.9
Difference-mean 2.0 (T=1.96; P=5–10%)		
1–4	38	31.3
5–15	44	29.1
Difference-mean 2.2 (T=2.61; P=0.5%)		

TABLE 2B

Age of Subjects	No. of Subjects	"Interstitial Space"* as Per Cent Body Wt. (mean)
0–0.5	8	33.1
0.6–1.0	6	25.6
Difference-Mean=7.5 (T=2.20; P=2.5%)		
0–1.0	14	29.9
1.1–6	29	22.4
Difference-Mean=7.5 (T=4.74; P=0.5%)		

* Interstitial Space (SCN-space−P.V.) as per cent of body weight.

Moreover, between the groups 0 to 1.0 versus 1.1 to 6 years, the differences are such that the T-value is 4.74 and P is only 0.5%.

Although adults show a sex difference in plasma and blood volumes as per cent of weight, it was not possible to demonstrate such differences in children. The average plasma and blood volume values obtained for 13 infants in the first year of life (table 3) were 50.3 cc./kg. and 80.0 cc./kg., respectively. Average values for all ages were 48.7 ± 10.2 cc. plasma/kg. and 81.1 ± 17.4 cc. blood/kg.

Discussion

In consideration of SCN-space as an approximation of extracellular water, a good deal of controversy centers around the use of correction factors. The serum concentration of SCN is supposedly 10% higher than interstitial levels.[22] Some of the SCN is bound

TABLE 3

Plasma Volume and B.V. in cc./kg./Body Weight for First Year (0–1) and for Age Group 0–9 Years

Age (Yr.)	No. of Subjects	cc./kg. body wt.		Standard Deviation
		(Range)	(Mean)	
0–1	13			
Plasma volume		31.8– 66.5	50.2	
Blood volume		55.4–116.0	80.0	
0–9	50			
Plasma volume		28.6– 84.2	48.7	±10.2
Blood volume		46.0–140.0	81.1	±17.4

to protein and lipid.[23–25] This portion tends to increase the measured serum level as some of the SCN is liberated in the serum precipitation step. Some SCN enters the red cell; some enters glandular cells; some very possibly enters into the intracellular compartment in pathologic states.[26,27] These factors of diffusion tend to decrease the serum level. The magnitude of these various factors is unknown. In consideration of this, and because determination of the relative size of the SCN-space at different ages was the principal objective of the present study, it was felt best to use no correction factors. The values are thus expressed in this paper as SCN-space, and this space is considered as only an approximation of the true extracellular compartment. Inasmuch as the SCN-space has been known to change in pathologic conditions,[28] occasionally to an extent suggesting considerable intracellular diffusion,[27] there exists the possibility that the rapid proportionate decrease in SCN-space during the first year of life may stem in part from a change in cellular permeability. However, to our knowledge there is no evidence which indicates that a change in the permeability relationships of the cell occurs as the body grows. There is evidence that Na^{24} and SCN both occupy fluid volumes of decreasing proportionate size with growth during early childhood.[13] The similarity of these changes in Na^{24} and SCN-spaces during growth suggests that although the SCN-space does not measure the true extracellular compartment, it probably reflects changes in that compartment with accuracy.

Of special interest is the relationship to age of SCN-space as per cent of body weight. Earlier studies in human beings[29-31] based for the most part on electrolyte measurements suggested that both total and extracellular water, as per cent of body-weight, decreased whereas intracellular water increased slightly with age. Moreover, Kerpel-Fronius[16] by the same methods emphasized this proportionate change in extracellular water as a progressive decrease. Using the SCN method in children, Robinow and Hamilton[2] and Doxiadis and Gairdner[15] verified these earlier reports. Morse and others,[14] on the other hand, found that although the calculated "interstitial space" decreased as per cent of body weight, the "extracellular space" did not. Unfortunately, their 65 cases ranged from 3 to 17 years of age, which excludes the period of infancy. Using both SCN and Na^{24} in 31 infants and children, Fellers[13] concluded that the decline in "extracellular space" was most rapid during the infancy period, with perhaps a secondary decline during adolescence. The observations in 108 subjects presented here show a rapid proportionate decrease in SCN-space over the first year of life with a break in the slope occurring at about one year; thereafter a tapering decrease obtains over the following years. This substantiates the findings of Fellers in the infancy period, although lack of sufficient observations in adolescence prevents comment concerning a secondary decline. Our values for space occupied by SCN start at about 40% of body weight and decrease to less than 30%. Adult values[19, 22, 32, 33] of 20 to 25% for the SCN method were not achieved by the older subjects up to 16 years of age.

Initially, total water content was determined by dessication studies.[29-31, 34-36] In rats, Hamilton[36] found a decrease from about 90% of body weight in early fetal life to 83% at birth and 70% in 40 to 60 days. Human fetus studies by Iob and Swanson[30] indicated a reduction in this total water from 95% to 75% at birth. The exact nature of postnatal decrease in total water content has remained speculative until the introduction of deuterium and antipyrine.[11, 37, 38] Investigation with these materials has supported the earlier total water values obtained by dessication studies. However, of most interest is the recent study by Friis-Hansen et al.[12] which indicates that this decline of total body water is most rapid in infancy. Their preliminary observations include only 24 subjects ranging in age from birth to 11 years but suggest a fall of 10 to 20% in total water as a per cent of body weight over roughly the first half year of life. This trend, if substantiated by further studies, correlates with the rapid decline of SCN-space and suggests that the decline in total body water is principally extracellular.

In light of the changes in SCN-space with growth the proportion of fat, the major variable in growing tissue[29, 39] and a substance low in water content, in the body is of interest. Adult humans have a fairly constant proportion of water when considered on a fat-free basis,[40] but in rats[34, 41] there is a decrease in this proportion during growth. As the percentage of fat is inversely proportional to specific gravity and as human growth is associated with an increase in specific gravity,[42] the young infant apparently has an even greater fat-free proportion of "extracellular water" compared to the older child.

Summary

Thiocyanate space was determined in 108 normal subjects and blood volume in 50 of these. These values are presented with relationship to physical indices of growth. The decrease in SCN-space as per cent of body weight is shown to be primarily in the first

year of life. The significance of this change is discussed with relation to total water and per cent of body fat.

ACKNOWLEDGMENT

The authors are grateful to John A. Anderson, M.D., Ph.D., Professor and Head of Department of Pediatrics, Stanford University School of Medicine, for his guidance in the study.

REFERENCES

1. Russell, S. J. M., Blood volume studies in healthy chidren, Arch. Dis. Child. **24**:88, 1949.
2. Robinow, M., and Hamilton, W. F., Blood volume and extracellular fluid volume in infants and children, Am. J. Dis. Child. **60**:827, 1940.
3. Morse, M., Cassels, D. E., and Schlutz, F. W., Blood volumes of normal children, Am. J. Physiol. **151**:448, 1947.
4. Kiss, P., and Teveli, Z., Die Absolute Blutmenge gesunder Kinder, Jahrb. f. Kinderh. **126**:339, 1929.
5. Seckel, H., Die Blutmenge Normalen ein- bis vierzehnjahriger Kinder, Jahrb. f. Kinderh. **127**: 149, 1930.
6. McIntosh, R., Determination of circulating blood volume in infants by carbon monoxide method, J. Clin. Investigation **7**:203, 1929.
7. Brines, J. K., Gibson, J. G., II, and Kunkel, P., Blood volume in normal infants and children, J. Pediat. **18**:447, 1941.
8. Darrow, D. C., Soule, H. C., and Buckman, T. E., Blood volume in normal infants and children, J. Clin. Investigation **5**:243, 1928.
9. Lucas, W. P., and Dearing, B. F., Blood volume in infants estimated by vital dye method, Am. J. Dis. Child. **21**:96, 1921.
10. Bakwin, H., and Rivkin, H., Estimation of volume of blood in normal infants and in infants with severe malnutrition, Am. J. Dis. Child. **27**:340, 1924.
11. Flexner, J. B., and others, Estimation of extracellular and total body water in newborn human infant with radioactive sodium and deuterium oxide, J. Pediat. **30**:413, 1947.
12. Friis-Hansen, B. J., Holliday, M., and Stapleton, T., Total body water in children, PEDIATRICS **7**:321, 1951.
13. Fellers, F. X., Barnett, H. L., Hare, K., and McNamara, H., Change in thiocyanate and sodium^{24} spaces during growth, PEDIATRICS **3**:622, 1949.
14. Morse, M., Cassels, D. E., and Schlutz, F. W., Available and interstitial fluid volumes of normal children, Am. J. Physiol. **151**:438, 1947.
15. Doxiodis, S. A., and Gairdner, D., Estimation of extracellular fluid volume by thiocyanate method in children and adults, Clin. Sc. **6**:257, 1948.
16. Kerpel-Fronius, E., Über die Besonderheiten der Salt- und Wasserverteilung im Sauglingskorper, Ztschr. f. Kinderh. **58**:726, 1937.
17. Gregersen, M. I., and Stewart, J. D., Simultaneous determination of plasma volume with T-1824 and "available fluid" volume with sodium thiocyanate, Am. J. Physiol. **125**:142, 1939.
18. Gregersen, M. I., Practical method for determination of blood volume with dye T-1824: Survey of present basis of dye method and its clinical applications, J. Lab. & Clin. Med. **29**:1266, 1944.
19. Stewart, J. D., and Rourke, G. M., On measurement of extracellular fluid volume with thiocyanate and body fluid analyses in 33 normal individuals, J. Lab. & Clin. Med. **26**:1383, 1941.
20. Barker, M. H., Blood cyanates in treatment of hypertension, J.A.M.A. **106**:762, 1936.
21. Morris, C. L. O. R., Chromatographic determination of Evan's blue in plasma and serum, Biochem. J. **38**:203, 1944.
22. Lavietes, P. H., Boudillon, J., and Klinghoffer, K. A., Volume of extracellular fluids of body, J. Clin. Investigation **15**:261, 1936.
23. Scheinberg, I. H., and Kowalski, H. J., Binding of thiocyanate to albumin in normal human serum and defibrinated blood with reference to determination of "thiocyanate space," J. Clin. Investigation **29**:475, 1950.
24. Rawson, R. A., Binding of T-1824 and structurally related diazo dyes by plasma proteins, Am. J. Physiol. **138**:708, 1943.

25. Rosenbaum, J. D., and Lavietes, P. H., Lipoid-thiocyanate in serum, J. Biol. Chem. **131**:663, 1939.
26. Overman, R. R., and Feldman, H. A., Effect of fatal P. Knowlesi malaria on simian circulatory and body fluid compartment physiology, J. Clin. Investigation **26**:1049, 1947.
27. Overman, R. R., Permeability alterations in disease, J. Lab. & Clin. Med. **31**:1170, 1946.
28. Stewart, J. D., and Rourke, G. M., Change in blood and interstitial fluid resulting from surgical operation and ether anesthesia, J. Clin. Investigation **17**:413, 1938.
29. Stearns, G., Mineral metabolism in normal infants, Physiol. Rev. **19**:415, 1939.
30. Iob, V., and Swanson, W., Mineral growth of human fetus, Am. J. Dis. Childhood **47**:302, 1934.
31. Hamilton, B., Relation between water and dry substance in human fetus: Example of constant differential growth ratio, Acta paediat. **18**:272, 1936.
32. Kaltreider, N. L., Meneely, G. R., Allen, J. R., and Bale, W. F., Determination of volume of extracellular fluid of body with radioactive sodium, J. Exper. Med. **74**:569, 1941.
33. Crandall, L. A., Jr., and Anderson, M. X., Estimation of state of hydration of body by amount of water available for solution of sodium thiocyanate, Am. J. Digest. Dis. & Nutrition **1**:126, 1934.
34. Hatai, S., Changes in composition of entire body of albino rat during life span, Am. J. Anat. **21**:23, 1917.
35. Harrison, H. E., Darrow, D. C., and Yannet, H., Total electrolyte content of animals and its probable relation to distribution of body water, J. Biol. Chem. **113**:515, 1936.
36. Hamilton, B., and Dewar, M. M., Relation between water and dry substance in body of rat, before and after birth, Growth **2**:13, 1938.
37. Soberman, R., and others, Use of antipyrine in measurement of total body water in man, J. Biol. Chem. **179**:31, 1949.
38. Moore, F. D., Determination of total body water and solids with isotopes, Science **104**:157, 1946.
39. Morales, M. F., Rathbun, E. N., Smith, R. E., and Pace, N., Studies on body composition. II. Theoretical considerations regarding major body tissue compartments, with suggestions for application to man, J. Biol. Chem. **158**:677, 1945.
40. Pace, N., and Rathbun, E. N., Studies on body composition. III. Body water and chemically combined nitrogen content in relation to fat content, J. Biol. Chem. **158**:685, 1945.
41. Moulton, C. R., Age and chemical development in mammals, J. Biol. Chem. **57**:79, 1923.
42. Boyd, E., Specific gravity of human body, Human Biol. **5**:646, 1933.

SPANISH ABSTRACT

El Crecimiento del Espacio del Tiocianato en la Infancia

Es escaso el conocimiento con respecto a los cambios de tamaño de los distintos compartimentos del agua orgánica durante el periodo de crecimiento del nacimiento a la madurez en el hombre o animales. En el niño existe cierta información acerca del crecimiento del volumen plasmático durante dicho periódo, pero solo hay algunas observaciones referentes al agua total del cuerpo, o del agua extracelular, pero la pobreza de información es extrema en lo concerniente a la naturaleza y rapidez de las alteraciones de estos compartimentos con el crecimiento. Efectivamente existen pruebas por estudios de desecación postmortem y en vivo que tanto el agua total del organismo como el agua extracelular decrece con la edad, siendo esta disminución mas rápida durante la infancia lo cual se correlaciona bien con la observación clínica de la hidrolabilidad de los lactantes comparada con niños de mayores edades y adultos, manifestada por sus requerimentos de agua proporcionalmente mayores y su gran susceptibilidad a los trastornos fisiológicos como la deshidratación, colapso circulatorio y desequilibrio ácido básico. La importancia pediátrica de este tipo de estudios es pues evidente y los autores reportan en este artículo los resultados obtenidos determinando la relación que existe entre el agua extracelular y la edad y los cambios de éste con aquella, usando el método del tiocianato de sodio que dá lo que se llama el "espacio del tiocianato," es decir, aproximadamente el del compartimiento extracelular, y el colorante azul de Evans para determinar el volumen plasmático. La diferencia de ambos dó el agua intersticial. Se hicieron las determinaciones del espacio del tiocianato en 108 niños normales y del volumen sanguíneo en 50 de estos niños.

Se encontró una disminución definitiva del espacio del tiocianato expresado en por ciento del

peso del cuerpo del nacimiento hasta alrededor de los 2 años de edad con una disminución gradual de entonces en adelante.

Es mas pronunciada en el primer año, siendo el valor promedio de los primeros 6 meses de 39% del peso del cuerpo y entre los 6 y 12 meses de 33% mientras que después del primer año el descenso es lento. Puesto que se sabe que el espacio del tiocianato cambia en condiciones patológicas, en ocasiones al grado de sugerir una difusión intracelular considerable, se ha pensado que un cambio de permeabilidad celular explique el hallazgo anterior, pero no hay prueba alguna que indique tal posibilidad durante el crecimiento. El agua total orgánica disminuye también rápidamente, de 10-20% del peso del cuerpo, durante los primeros 6 meses de la vida segun estudios de Friis-Hansen y colaboradores, lo que de comprobarse por investigaciones posteriores sugiere que este descenso rápido del agua total es principalmente extracelular ya que se correlaciona bien con la rápida declinación del espacio del tiocianato en dicho periodo.

Es interesante, a la luz de estos cambios del espacio del tiocianato con el crecimiento, relacionar con ellos la proporción de grasa que es la variable mayor de los tejidos en crecimiento y al mismo tiempo una substancia de bajo contenido en agua. Si el crecimiento humano está asociado con un aumento en densidad y el porcentaje de grasa esta en razón inversamente proporcional a la densidad, el lactante tiene aparentemente una proporción aun mayor de "agua extracelular" libre de grasa que el niño mas grande.

1940 South Second East

PROGNOSIS OF PALSIES FROM CRANIAL NERVE INVOLVEMENT IN POLIOMYELITIS

By HANS U. ZELLWEGER, M.D.,* AND E. GABATHULER, M.D.
Zurich, Switzerland

THE prognosis of poliomyelitis is modified considerably by involvement of the brainstem and especially the bulbar centers. In the Children's Hospital, Zurich, 1264 cases have been observed during the years 1932-1948. Of these, 551 were non-paralytic cases and are not included in the present paper. Seven-hundred thirteen cases showed spinal paresis and/or encephalitic and/or bulbo-ponto-mesencephalic symptoms. The distribution of the different symptomatic groups and their early prognosis is shown in table 1.

TABLE 1

EARLY PROGNOSIS OF POLIOMYELITIS: CONDITION AT DISCHARGE OF PATIENTS (45–90TH DAY OF ILLNESS)

Cases	With Spinal Paralysis		With Pure Encephalitic Symptoms		With Bulbo-pontomesencephalic Symptoms	
	No.	%	No.	%	No.	%
Cured	121	26.8	18	82.1	110	45.7
Improved	285	63.2	3	13	63	26.5
Not improved	20	4.4	—	—	16	6.6
Died	25	5.6	1	5	51	21.2
	451	100	22	—	240	100

It is well known that the mortality rate in bulbar cases is far higher than in other forms of poliomyelitis. If patients with bulbar poliomyelitis live, the tendency to heal seems to be far greater than for those with spinal paralysis. If the fatal cases are taken out of consideration, it is noted that 58.2% of the patients with bulbo-pontino-mesencephalic symptoms were completely recovered at discharge whereas in only 28.4% of the cases had the spinal paralysis disappeared.

The early prognosis of the palsies from the individual cranial nerve involvement is recorded in table 2. Patients with bilateral palsy from one nerve are recorded as one case. If a patient had several cranial nerves involved, he is recorded in each of the corresponding columns. The patients were checked between the 45th and 90th day after onset at the day of discharge from the hospital.

Except the palsies of the soft palate and those from involvement of the sixth nerve, the palsies from involvement of cranial nerves disappeared within three months in more than half of the patients. The best early prognosis was seen in swallowing palsy, and in involvement of the oculomotor (III) and hypoglossal (IV) nerve palsy; whereas the early

From the Children's Hospital and University Children's Clinic, Zurich, Switzerland.
(Received for publication Feb. 1, 1952.)

* Present address: American University of Beirut, Beirut, Lebanon.

TABLE 2

EARLY PROGNOSIS OF PALSIES FROM POLIOMYELITIS OF CRANIAL NERVE: DETAILS PRESENTED FOR INDIVIDUAL NERVES

	Cranial Nerve Involved								
	Facial (VII)	Swallowing (X)	Soft Palate (X)	Abducens (VI)	Pupillary Symptoms (III)	Hypo-glossal (XII)	Oculo-motor (III)	Trochlear (IV)	Motor Trigeminal (V)
Total no. of patients with uni- or bilateral palsy	193	74	57	26	23	15	7	2	2
No. of deaths abs.	31	34	14	4	9	3	1	—	—
No. of deaths %	16	45.9	24.6	15.4	36.5	20	14.5	—	—
No. of living patients with uni- or bilateral palsy	162	40	43	22	14	12	6	2	2
Cured at discharge (45th–90th day)									
No. of patients	102	38	18	9	11	10	5	2	1
In % of living patients	63	95	42	41	79	83	83	—	—

prognosis of facial palsies is not quite as favorable. Sixty-eight per cent of living patients with isolated facial palsy and no other paralysis were cured at discharge, whereas only 59% of the patients in whom the facial palsy was combined with other bulbar or encephalitic symptoms and/or spinal paralysis were cured at discharge.

On the other hand the mortality is very high in cases with cranial nerve involvement because the bulbar centers for respiration and vasomotor control are more often involved than in spinal cases. The mortality rates recorded in table 2 are so uniformly higher than the rates for spinal cases in table 1 that the occurrence of involvement of a cranial nerve seems to be of prognostic value.

LATE PROGNOSIS OF PALSIES IN CRANIAL NERVE INVOLVEMENT

Very few figures are known about the late prognosis of poliomyelitic paralysis.

Insofar as spinal cases are concerned, Mustard[1] stated that in 40% residual paralyses are present; with adequate management and therapy 75% of the cases can be made completely independent, whereas 25% show residuals of such a degree, that it is necessary to supply braces and/or surgery.

The late prognosis of palsies from cranial nerve involvement has been studied by McQuarrie.[2] He found that between 14 and 17 months after the onset of definite paralysis of the palatine, facial or laryngeal muscles, there were significant degrees of residual impairment of motor function in from 18 to 77% of cases depending upon which nerve was affected.

Insofar as facial palsy is concerned, Schuhmacher[3] found 12 to 18 months after onset complete recovery in 18 cases, slight evidence of facial palsy in 14 cases, and marked palsy in one case. In a follow-up examination of 23 cases of facial palsy performed two years after onset, Rascoff[4] found all but one cured.

Considering these few experiences it seemed worth while to follow up the patients reported here. Since the greatest improvement of poliomyelitis palsies occurs within the first two years after onset, the authors limited the follow-up studies to those cases with onset of two years or more previously.

The results are shown in table 3. At time of discharge from the hospital 67 patients

TABLE 3

FINDINGS ON PATIENTS WITH CRANIAL NERVE INVOLVEMENT 2 TO 18 YEARS AFTER ONSET OF PALSY

	Facial (VII)	Swallowing (X)	Soft Palate (X)	Abducens (VI)	Pupillary Symptoms (III)	Hypo-glossal (XII)	Motor Tri-geminal (V)
No. of cases	37	2	19	5	3	2	1
Cured	16	—	3	4	2	2	—
Much improved	11	2	7	—	—	—	1
Slightly or not improved	10	—	9	1	1	—	—

had presented together 107 cranial nerve lesions. Fifty-nine patients with 69 palsies have been re-examined between 2 and 18 years after onset. Thirty-nine patients with 48 palsies were completely or nearly completely cured; in 20 patients 21 palsies were still present; 10 facial palsies, 9 palsies of the soft palate, one palsy from a lesion of the sixth nerve and one palsy of the pupillary sphincter of one eye. One of the 10 facial palsies was still severe with definite deviations of the mouth, whereas in the 9 others deviations could only be seen if the patients were laughing or crying. The 9 palsies of the soft palate were slight; contractions were incomplete and asymmetric, when the gag reflex was elicited, 4 of them had a rhinolalia, but all could swallow fluids and solid foods without any trouble. The only palsy from the sixth nerve was severe, but did not hamper the patient in his work.

Ten patients in whom 38 cranial nerve lesions were involved could not be re-examined; 31 of them were even much improved at discharge. Therefore it is possible that the palsies have disappeared completely; the seven remaining with palsies were more severe at discharge; unfortunately they could not be followed up.

SUMMARY

Seven-hundred thirteen cases of poliomyelitis with spinal paralysis, encephalitic or bulbar symptoms are reviewed. The mortality rate in bulbar cases was four times that in spinal cases, whereas early recovery after bulbar symptoms was twice that of spinal paralysis.

A follow-up study of 59 patients with 69 palsies from cranial nerve injury performed 2 to 18 years after the acute stage showed that 39 patients with 48 palsies were cured; 18 patients had together 19 palsies of minor degree. Two patients, one with involvement of the sixth and one with involvement of the seventh cranial nerve had more severe sequelae. None of the palsies affected the life of the patients.

Thus if patients with cranial nerve involvement stay alive the late prognosis is much better; the majority of the palsies disappear, the remaining ones have no crippling effect for the patient.

REFERENCES

1. Mustard, H. S., Questions and Answers About Polio, New York, National Foundation for Infantile Paralysis, Inc., 1949.
2. McQuarrie, I., in Poliomyelitis, Philadelphia, J. B. Lippincott Company, 1949.
3. Schuhmacher, P., Zur Prognose der Fazialislähmung bei Poliomyelitis, München med. Wschnschr. **87**:591, 1940.
4. Rascoff, H., Prognosis of facial nerve paralysis in poliomyelitis, J. Pediat. **35**:567, 1949.

SPANISH ABSTRACT

Pronóstico de las Parálisis de los Nervios Craneanos en la Poliomielitis

Los autores del trabajo revisaron 713 casos de poliomielitis con parálisis espinal y bulbar. La mortalidad en los casos bulbares fué 4 veces mayor que en los espinales en tanto que la recuperación temprana de los síntomas bulbares fué 2 veces mas frecuente que la de las parálisis espinales. Excepción hecha de las parálisis del velo del paladar blando y del sexto par craneano, las otras variedades de parálisis craneanas desaparecieron dentro de los 3 primeros meses, en mas de la mitad de los enfermos. Las de mejor pronóstico temprano fueron las parálisis de la deglución, del nervio oculomotor e hipogloso en contraste con las parálisis del facial pues el 68% de los casos con parálisis facial exclusivamente estaban curados entre el 45° y 90° día, al salir del hospital, y solamente el 59% de los casos en que aquella coexistía con síntomas bulbares o encefalíticos, combinados o no con parálisis espinal.

Con respecto al pronóstico tardío o lejano de las parálisis craneanas encontraron que de 59 pacientes con 69 parálisis 39 de ellos que tenían 48 parálisis habían curado entre el 2° y 18° año después del periódo agudo. De los otros 20 casos restantes 18, que tenían en total 19 parálisis las presentaban aun pero en grado ligero, y solo 2, uno con parálisis del sexto par y otro del séptimo las tenían aun en forma severa. De los 18 casos que tenían parálisis aunque en forma ligera 9 eran parálisis del facial y solo era apreciable cuando el enfermo reía o lloraba, y los otros 9 eran del velo del paladar manifestandose por su contracción incompleta y asimétrica, en 4 de ellos por rinolalia, pero ninguno tenía dificultad para tomar líquidos o deglutir alimentos sólidos.

En la revisión de la literatura encuentran que el 40% de los casos espinales quendan con parálisis residuales y de ellos, el 75%, con tratamiento adecuado, no requieren de la cirugía u aparatos. Por lo que respecta a los casos con parálisis de los nervios craneanos, de un 18 al 77% de ellos, dependiendo del tipo de parálisis; palatina, facial o laringea, presentaban un grado significativo de interferencia motora residual entre el 15° y 17° meses después del principio franco de la parálisis. Con referencia a la parálisis facial en particular, de 33 casos revisados entre 12-18 meses del principio, 18 curaron por completo, 14 la presentaban en grado ligero y en solo 1 existía en forma acentuada. En otro grupo de 23 casos, todos curaron con excepción de uno de ellos, a los 2 años de instalarse.

Los autores concluyen, que si los enfermos con parálisis craneanas sobre viven, el pronóstico tardio es mucho mejor desapareciendo la mayor parte de las parálisis y las que permanecen no producen invalides en el paciente.

Children's Hospital

TUBERCULOSIS OF CERVICAL LYMPH NODES

By ORVAR SWENSON, M.D., AND WILFRED T. SMALL, M.D.
Boston

CERVICAL tuberculous adenitis, a children's disease common 50 years ago, is now a rare condition in the United States. The decreased incidence is probably due in large measure to the eradication of bovine tuberculosis, and to the use of pasteurized milk, sanitorium care of tuberculous patients with open lesions, and improved living conditions. In 1917, Ladd predicted that this disease would be controlled by public health measures.[1]

No disease has a more colorful history. Edward the Confessor introduced the "King's Touch," which consisted in a digital tapping of the diseased neck by the monarch. It became so popular that Charles II is said to have touched 10,000 sufferers a year,[2] and it continued in vogue for more than six hundred years. At the beginning of the present century, surgical excision of the diseased glands was demonstrated to be an effective method of treatment. Today, the disease is so rare that physicians unfamiliar with the excellent results in children after complete surgical excision of the glands have been prone to prescribe streptomycin, but in the authors' experience this drug has been of little value unless operation is performed.

The common route of infection of the cervical glands is by way of the tonsils. The infection may also enter by way of the adenoids, and in such cases the preauricular glands and those of the posterior triangle are most likely infected secondarily. The lesions in the glands are secondary, and therapy directed at them alone is therefore doomed to failure, unless supplemented by eradication of the primary lesions.

SUMMARY OF CASES

Case 1: This 6 yr. old boy entered the hospital because of swelling, of 10 wk.' duration, beneath the right mandibular angle. During the 2 wk. prior to admission the area became red and soft. Exudate was aspirated from the inflamed gland, and smears of this contained acid-fast bacilli. An intracutaneous tuberculin test was positive, and a chest roentgen film was normal. To prevent spontaneous perforation of the red skin over the glands, excision was performed despite the presence of enlarged tonsils. The pathologic diagnosis on the tissue was tuberculosis. A draining sinus developed postoperatively, and small amounts of seropurulent material drained for 3 wk., after which time the sinus closed spontaneously. Sulfadiazine and penicillin were administered to the patient during the 3 wk. period. Tonsillectomy and adenoidectomy were performed 4 wk. later. Six years after operation the patient was in excellent health and had no evidence of recurrence. Despite a slight excavation of the subcutaneous tissue at the operative site, the cosmetic result was good.

Case 2: This 5 yr. old girl entered the hospital because of swelling, of 11 mo.' duration, in the submaxillary region. Tonsillectomy had been performed 8 mo. prior to admission, and the swelling subsided slightly after the operation, only to increase 6 mo. later. Exudate was aspirated from the gland, and smears of this contained acid-fast bacilli. The patient had been drinking unpasteurized milk. An intracutaneous tuberculin test was positive, and a chest RG was negative. After the glands were aspirated, a draining sinus developed. Excision of the tuberculous glands and sinus was performed. The wound healed without the formation of a draining sinus. Four and a half years later the patient was in good health without evidence of recurrence, and the cosmetic result was good.

From The Boston Floating Hospital (for Infants and Children) and the Department of Surgery, Tufts College Medical School, Boston.

(Received for publication Jan. 22, 1952.)

Case 3: This 4 yr. old boy entered the hospital because of a mass, of 4 mo.' duration, overlying the right parotid region. The area had never drained, but was rapidly becoming red and fluctuant. There was a history of exposure to tuberculosis. An intracutaneous tuberculin test was positive, and a chest RG was normal. Because of the location of the mass, a sialogram was performed revealing a normal parotid with a mass outside the gland. A small amount of thick, purulent material was aspirated from the gland; and on smear, acid-fast bacilli were demonstrated. A draining sinus developed, and the patient was readmitted. At this time partial excision of the mass and sinus was performed. Streptomycin, 1 gm. daily, was administered for 3 wk., after which drainage subsided; and the wound healed by secondary intention. Twenty-one months later the patient was in excellent health without evidence of recurrence.

Case 4: This 4 yr. old boy entered the hospital because of a mass anterior to the right ear and a mass below the angle of the right mandible. Both swellings were of 2 mo.' duration. A patch test for tuberculosis was positive, and a chest RG was normal. Despite a 2 wk. course of streptomycin therapy, the glands enlarged. Excision of the matted, caseous lymph nodes was performed, and the incisions healed without sinus formation. Ten months following excision the patient was well and had a good cosmetic result. Postoperatively the patient received streptomycin, 1 gm. daily for 2 wk.

Case 5: This 7 yr. old girl was seen in consultation because of a fluctuant area over the left parotid gland. The swelling was aspirated and a moderate amount of thin purulent material obtained. This was found to contain tubercle bacilli by guinea pig inoculation. A tuberculin patch test was negative, as was a chest RG. The gland continued to drain despite streptomycin treatment given during a 4 wk. period (1 gm./day was administered). Several months later the sinus closed leaving an irregular scar. A few months later a second gland developed lower in the neck. It drained, and again streptomycin was administered with termination of drainage several weeks later. The cosmetic result was not satisfactory.

Case 6: This 14 yr. old girl entered the hospital because of a mass, of 2 mo.' duration, in the left side of the neck. She had recent contact with one known to have tuberculosis. Tonsillectomy and adenoidectomy had been performed at the age of 6 yr. An intracutaneous tuberculin test was positive, and a chest RG was negative. Excision of the mass, which at operation was found to be a group of matted, caseous lymph nodes, was performed. Acid-fast bacilli were demonstrated on smear from the tissue removed at operation. An accumulation of fluid in the wound made it necessary to perform 5 aspirations during the 1st 10 days after operation. The wound healed without a sinus forming. Four months following operation, there was no evidence of recurrence. The incision was soft and pliable and scarcely visible.

Case 7: This 5 yr. old girl entered the hospital because of a left cervical swelling of 2 mo.' duration. The swelling had been nontender, but shortly before admission the area became fluctuant and red. There was danger of spontaneous perforation of the skin. The patient had been treated with penicillin, aureomycin, and intermittent bedrest. The child appeared chronically ill and had some temperature elevation. An intracutaneous tuberculin test was positive, and a chest RG was negative. The patient's mother had recovered from tuberculosis, and a maternal uncle had died of tuberculosis. Examination of the patient revealed a firm fixed mass with central fluctuation in the left submandibular area, measuring 5 by 3 cm. The overlying skin was thin, shiny and red. A node dissection was performed, and the involved skin was removed with the specimen. The patient was placed on streptomycin for 1 mo., and after this the tonsils and adenoids were removed. The incision healed without a sinus forming. A pathologic diagnosis of tuberculosis was made on tissue removed at operation. Four months after operation the patient was doing well and had a good cosmetic result.

Case 8: This 8 yr. old boy entered the hospital because of a nontender swelling of 1½ yr.' duration, in the submental area. No drainage or inflammation was visible. A tonsillectomy had been performed at 3 yr. of age. An intracutaneous tuberculin test was positive. There was no known contact with tuberculosis. Chest RG was negative. Examination revealed a small, circumscribed, hard, nontender mass in the submental area. Operation was performed with excision of the matted nodes. Pathologic diagnosis on the removed glands was caseous tuberculosis. The patient received streptomycin postoperatively. The incision healed without sinus formation, and the cosmetic result was good.

Case 9: This 3 yr. old girl entered the hospital because of a lump, of 3 mo.' duration, on the left side of the jaw. The patient had been treated previously with penicillin, sulfadiazine and aureomycin. The swelling decreased in size and remained as a marble-sized mass. Prior to admission the

swelling became red and slightly fluctuant. An intracutaneous tuberculin test was positive. Twelve years previously a tuberculous gland had been removed from the neck of a maternal grandmother. The child was operated on, and excision of the involved nodes on the left side of the neck was performed. The wound healed by first intention. The patient was placed on streptomycin for 2 wk. postoperatively, after which tonsillectomy and adenoidectomy were carried out. Two months later she was doing well, and there was no evidence of recurrence.

Case 10. This 22 mo. old girl had an enlarged gland under the chin, which appeared 1 mo. before admission as a painless swelling and which slowly increased in size. Other enlarged glands appeared on each side of the neck. There was no history of contact with tuberculosis or ingestion of raw milk. The glands were matted together and fixed to the skin and deep structures. An intracutaneous tuberculin test was positive, and chest RG was negative. Aspiration of one soft gland yielded exudate, and on smearing it, acid-fast bacilli were found. Tonsillectomy and adenoidectomy were performed. Three weeks later the child was readmitted because the glands were larger, and bilateral neck dissection was performed. The wound healed satisfactorily, and the child was discharged on the tenth postoperative day.

Case 11. This 8 yr. old girl entered the hospital because of a hard mass, of 19 mo.' duration, beneath the left mandible. There had been intermittent drainage from a sinus in the center of the mass. A course of penicillin therapy was given for 1 wk. in the initial stage of the disease. Fifteen months prior to admission incision and drainage was performed, and intermittent drainage occurred during this period. She was given a course of roentgen therapy which resulted in a slight diminution in the size of the mass. Eight months before entry the drainage became more profuse. She was given streptomycin for 6 wk. A course of aureomycin followed 4 mo. later. Tonsillectomy and adenoidectomy were performed. An intracutaneous tuberculin test was positive, and chest RG was negative. Unpasteurized milk had been consumed by the patient. On admision, there was a draining sinus surrounded by matted glands on the left side of her neck. An excision of the glands including the sinus tract was performed. Acid-fast bacilli were abundant in the tissue removed, and a pathologic diagnosis of tuberculosis was made. A wound hematoma developed, and small amounts of serosanguineous fluid drained from the wound for 10 days postoperatively. Streptomycin, 1 gm. daily, was given for 2 wk. beginning immediately after operation. When the patient was seeen 22 mo. later, there was no evidence of recurrence; and the cosmetic result was good.

Diagnosis

Early in the course of cervical tuberculous adenitis, diagnosis is difficult because the gland is discrete, without evidence of inflammation; and it is difficult to distinguish it from a gland enlarged with pyogenic infection or some form of malignant disease. Later the diagnosis of cervical tuberculous adenitis is less difficult, providing the disease is kept in mind. A diagnosis of tuberculous cervical adenitis should be made when a child has unilateral, matted, nontender cervical glands of six weeks' or more duration and a positive intracutaneous tuberculin test. A history of contact with tuberculosis or ingestion of raw milk is further evidence that helps confirm this diagnosis. The disease must be differentiated from lymphosarcoma and Hodgkin's disease. Glands containing malignant disease are usually bilateral and disseminated. They are discrete and unattached to the skin and deep structures, and the patient usually has a negative intracutaneous tuberculin test. Often there is splenic enlargement. A skin tuberculin was positive in all but one of these patients. It is important to note that this was a skin patch test. Had an intracutaneous tuberculin test been performed, it may well have proved to be positive. A negative intracutaneous test, when the dilution of old tuberculin has been one to one hundred or less, with proved cervical tuberculosis is rare; and such a finding usually precludes the diagnosis of tuberculous adenitis.

Treatment

Tonsillectomy and adenoidectomy should be performed on all patients with cervical

tuberculous adenitis. If enlarged neck glands are present two weeks after this, they should be excised. Only in instances when the skin is thin and red over the glands and spontaneous drainage is imminent should tonsillectomy be deferred until after excision of the glands.

In patients with cervical tuberculous adenitis on whom tonsillectomy and adenoidectomy have been performed before the onset of the cervical adenitis, careful attention should be given to other possible portals of entry; and then excision should be performed.

Tuberculous glands of the neck should not be removed by a block dissection such as that used for glands containing metastatic malignant implants. In tuberculosis excellent results are secured by excision of the glands alone, and no other structure need be sacrificed or damaged. A transverse incision in a skin fold gives adequate exposure and an excellent cosmetic result.[3] The incision parallel to the sternocleidomastoid muscle

FIG. 1. A patient with tuberculous adenitis with redness of skin. B. Same patient 2 mo. later. Primary healing took place despite contamination of wound with exudate.

should not be used, for a prominent, diagonal, unsightly scar often results. If a sinus is present, or the skin is thin and red, an elliptic incision is used so that the sinus or devitalized skin can be removed with the glands (Fig. 1). There is an intense periglandular inflammation about the superficial glands so that they are matted together and adherent, requiring sharp dissection in their removal. Occasionally, caseous glands are inadvertently broken and the operative field contaminated with exudate. This is tolerated perfectly well by the tissue, and primary healing is the rule in such situations.

In the dissection of the superficial glands, care must be exercised to prevent damage to the inframandibular branch of the facial nerve. This branch swings down the neck considerably below the mandible and is of such size that visual identification is almost impossible. Utilization of an electric stimulator as the region of the nerve is approached, with the anesthetist observing the face, will identify the area of the nerve and thus safeguard it from damage. Cutting of the nerve results in dysfunction of the angle of the mouth, which is objectionable. The spinal accessory nerve should be isolated after the superficial glands have been dissected free. It is a large nerve and easily identified by dissecting along the anterior border of the sternomastoid muscle in the upper third. The nerve is usually superficial to the internal jugular vein and descends obliquely behind the digastric and stylohyoid muscles to enter the upper part of the sternocleidomastoid

muscle. Cutting of this nerve in a child usually results in a painful, depressed shoulder in later life.

As the carotid sheath is exposed, the glands are smaller, less adherent, and are more easily removed. All glands that are identified should be removed to prevent recurrence. The hypoglossal nerve should be recognized as it emerges between the internal carotid artery and the internal jugular vein, and swings forward and downward and becomes superficial below the digastric muscle. Damage to the nerve produces ipsilateral deviation and atrophy of the tongue. When all visible and palpable glands have been removed, complete hemostasis is secured by the use of fine catgut ligatures. The wound is closed

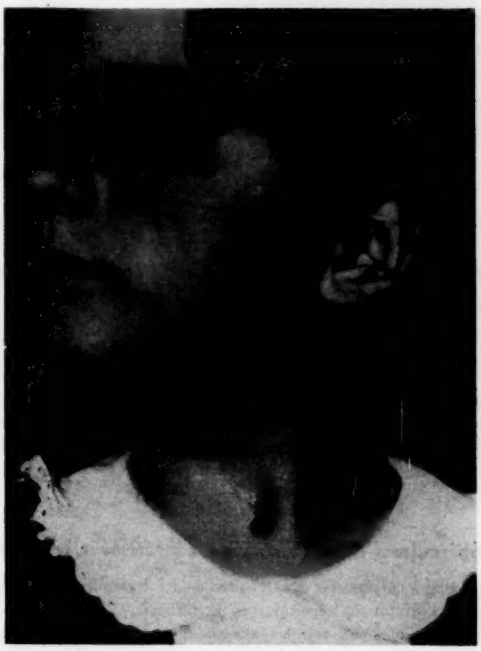


FIG. 2. Patient treated with streptomycin. Note preauricular scar and second drainage area.

with interrupted silk sutures to the skin without drainage. A drain should not be left in the wound because it promotes the formation of a sinus. Should fluid collect in the wound postoperatively, repeated aspirations until fluid no longer accumulates is recommended.

DISCUSSION

Three of these 11 patients were treated with streptomycin preoperatively. In two of these patients, the results were complete failures and required subsequent surgery for control of the disease. One patient treated with streptomycin had a chronic draining sinus, a poor cosmetic result, and a recurrence (Fig. 2). This patient has not been operated upon. The prolonged series of painful injections was of some hazard and inconvenience to these patients. The chronic draining sinus in these patients was bother-

some and probably dangerous because acid-fast organisms are usually present in the discharge.

The 10 patients whose diseased glands were removed had good results. One patient had slight drainage for three weeks, which was probably attributable to the fact that a drain was used in the wound. One patient whose diseased preauricular gland was incompletely removed had drainage in small amounts for three weeks. This demonstrates the importance of complete removal of all involved glands.

Three patients had involvement of the preauricular nodes which clinically could not be distinguished from a tumor of the parotid gland. Sialograms were performed on two patients, and they demonstrated the mass to be outside the parotid tissue.

In none of these patients was there any postoperative evidence of nerve damage. Streptomycin, while not always effective alone, may be of some value in the prevention of postoperative complications.[4] In these cases streptomycin, 1 gm., was usually given daily for two weeks postoperatively. However, the results with the use of streptomycin postoperatively are no better than those reported by Ladd in 1917.

Summary

Although these results were determined in a small group of patients, it is believed they indicate that surgical excision is the best treatment for cervical tuberculous adenitis.

Streptomycin, which may fail as a lone therapeutic agent, may be of value as a postoperative adjunct to surgery.

References

1. Ladd, W. E., Tubercular cervical adenitis in children, Surg., Gynec. & Obst. **24**:467, 1917.
2. Bailey, H., Cervical adenitis, Lancet **1**:313, 1948.
3. Dowd, C. N., Tuberculosis of cervical lymphatics: Study of 687 cases, J.A.M.A. **67**:499, 1916.
4. Lester, C. W., Tuberculosis of cervical lymph nodes: Present surgical status, Surg., Gynec. & Obst. **87**:719, 1948.

Spanish Abstract

Tuberculosis de los Ganglios Linfáticos Cervicales

El objecto de este trabajo es reportar los resultados del tratamiento quirúrgico de 11 casos de tuberculosis de los ganglios linfáticos cervicales en la infancia.

La vía mas común de la infección son las amígdalas aunque las adenoides también, y en este caso los ganglios preauriculares y del tríangulo posterior son los que mas probablemente se infectán secundariamente. Por consiguiente la terapeútica no debe dirigirse exclusivamente a los ganglios infectados sino tambíen a las lesiones primarias advocándose la extirpación quirúrgica tanto de los ganglios como de adenoides y amígdalas. Si dos semanas después de la adenoamigdalectomía los ganglios cervicales persisten aumentados debe hacerse su extirpación a menos que la piel circunoccina esté roja y adelgazada y su abertura espontanea sea inminente en cuyo caso la tonsilectomía debe hacerse posteriormente a la extirpación ganglionar. Si el enfermo desarrolla su adenitis cervical tuberculosa estando carente de adenoides y amígdalas deben buscarse cuidadosamente otras puertas de entrada posibles y hacer su excisión. La extirpación ganglionar no debe hacerse por disección en masa como se practica la de los ganglios con metástasis tumorales sino exclusivamente de los nódulos.

Tres de los 11 enfermos se trataron con estreptomicina antes de la operación, dos de ellos con fracaso completo y requirieron la extirpación para ser curados, el otro presentó una fístula crónica con un resultado cosmético lamentable y recaída.

Además del inconveniente de las numerosas inyecciones dolorosas y la molestia de la fístula, esta representa un peligro porque generalmente la secreción que escurre tiene bacilos tuberculosos.

Los resultados obtenidos en los enfermos operados fueron buenos. Dos casos tuvieron un poco de secreción por cerca de 3 semanas, uno por haberse drenado la herida y el otro por extirpación incompleta del ganglio preauricular lo cual enfatiza la importancia de hacerlo en forma completa. En ningún caso hubo lesión de troncos nerviosos. Aunque aparentemente el uso de estreptomicina a la dosis de un gramo diario por las dos primeras semanas del postoperatorio parece ser satisfactoria, no mejora los obtenidos por otro autor sin su empleo.

El autor concluye que aunque el número de casos es pequeño, la excisión quirúrgica es el mejor tratamiento de la tuberculosis ganglionar cervical y que la estreptomicina que puede fallar como agente terapeútico único, puede ser de valor como coadyuvante postoperatorio.

20 Ash Street

FULMINATING MENINGOCOCCEMIA TREATED WITH CORTISONE; USE OF BLOOD EOSINOPHIL COUNT AS A GUIDE TO PROGNOSIS AND TREATMENT

By HORACE L. HODES, M.D., RALPH E. MOLOSHOK, M.D., AND MILTON MARKOWITZ, M.D.
New York City

LAMS[1] in 1907 reported that the number of eosinophils in the blood rises during convalescence from disease and hence might be used as a means of prognosis. More recently, Dalton and Selye[2] have shown that eosinopenia is a characteristic part of the "alarm" reaction. In 1948 Thorn and his coworkers[3] reported that the administration of ACTH (adrenocorticotrophic hormone) to persons with normal adrenocortical function is followed by a rapid decrease, exceeding 50%, in the total circulating eosinophil count, and that ACTH brings about very little, if any, decrease in the blood eosinophils of patients with Addison's disease. These authors concluded that the blood eosinophil count is a reliable index of adrenocortical function. This observation has been supported by Hain[4] who reported that 29 children, with apparently normal adrenocortical reserve, undergoing stress in the form of acute infection, exhibited blood eosinophil counts ranging from 0 to 97/cmm. in contrast with a range of from 109 to 359 among normal healthy children. The present investigators have obtained similar data among infants and children suffering from acute infectious diseases. Eosinophil counts made on the blood of 18 patients on the day of admission to the hospital for the treatment of rubeola, pneumococcic pneumonia and diphtheria have ranged between 0 and 25/cmm. in contrast with a range of from 125 to 300 among 15 normal children. Faloon, Reynolds and Beebe[5] reported that serial eosinophil counts proved to be of value during the course of treatment of a patient with meningococcic meningitis who presented symptoms of the Waterhouse-Friderichsen syndrome. They stated that the blood eosinophil level furnished an index of adrenocortical response and was of aid in the regulation of therapy with adrenocortical extract.

Clinical evidence and necropsy findings have led to the suggestion that acute adrenal insufficiency plays an important role in the production of the Waterhouse-Friderichsen syndrome during the course of meningococcemia and that it is largely responsible for the high mortality rate in this condition. It has been generally considered that hemorrhage into the adrenal cortex is the underlying cause of adrenal failure, but Williams[6] and Ferguson and Chapman[7] have called attention to the absence of gross adrenal hemorrhage at postmortem examination in several patients with clinical findings indistinguishable from those in which adrenal hemorrhages were found. Rich[8] has reported that extensive focal necrosis of the adrenals is found in some cases in the absence of hemorrhages. It is known that acute stress depletes the adrenal cortical cells of lipoid material and it has been suggested that this may increase the susceptibility to degenerative

From the Department of Pediatrics of The Mount Sinai Hospital, New York City, and The Harriet Lane Home, The Johns Hopkins Hospital, Baltimore, Md.
(Received for publication Feb. 26, 1952.)

changes.[9] The use of adrenal cortical extracts in the treatment of fulminating meningococcemia has been advocated in several reports[9–13] although the efficacy of such therapy was considered to be dubious.

Fatalities among infants and children with meningococcemia and meningitis at the present time are to a large extent limited to patients showing evidence of circulatory collapse and shock. Some of these patients enter the hospital exhibiting obvious signs of such collapse. In other instances, a period of apparent well-being may be followed by the sudden appearance of pallor, collapse and death. At the onset of infection in some cases we are unable to predict the outcome with assurance. It seemed to the authors that serial estimations of the function of the adrenal cortex might yield information of value in the prognosis and consequently in the treatment of patients with meningococcemia and meningitis. It was thought that such information might make it possible to detect evidence of adrenal insufficiency before the onset of clinical collapse and to take steps to prevent such an eventuality. The serial estimation of the circulating blood eosinophil level was chosen as a test of adrenocortical function most likely to be of practical value. It was supposed that a low blood eosinophil count early in the course of meningococcus infection could be interpreted as indicative of an adequate adrenal response. On the other hand an eosinophil count within the normal range in the face of severe infection might indicate a lack of adequate adrenal function.

Experience with Eosinophil Counts in Meningococcal Infection of Mild or Moderate Degree

During 1948 and 1949 serial blood eosinophil counts were made on eight patients with meningococcic sepsis or meningitis, as indicated in chart 1. Six of these patients were considered to be suffering from an illness of average severity, while two were mildly ill on admission. In no instance was the patient's condition critical, and none of the children exhibited any evidence of shock or other signs suggestive of the Waterhouse-Friderichsen syndrome. Seven of the patients had received no specific treatment before admission. On admission to the hospital, the blood eosinophil count was found to be 0/cmm. in 6 patients; an initial count of 25/cmm. was found in a seventh patient. A rise in the number of eosinophils toward normal values occurred during convalescence. As indicated in chart 1, normal values were reached between the third and seventh day after beginning treatment. All seven children recovered without sequelae.

The eighth patient studied entered the hospital after two days of treatment, when he was obviously convalescent (chart 1). His blood contained 100 eosinophils/cmm. on admission with a rise to 175 on the following day. Since the child was in a recovery phase at the time these normal eosinophil counts were obtained, it was assumed that they were indicative of a rebound phenomenon of convalescence rather than adrenal insufficiency. This interpretation was put to the test by the administration of 10 mg. ACTH. As shown on chart 1, within six hours there was a sharp decrease in the eosinophil count from 178 to 65/cmm. This result is indicative of normal adrenocortical reserve and supported the estimate of the situation. The child made a rapid, complete recovery.

Experience with Fulminating Meningococcal Infection

In the eight cases described above the eosinophil response was that which would be expected of children whose adrenocortical function is adequate. None of them appeared

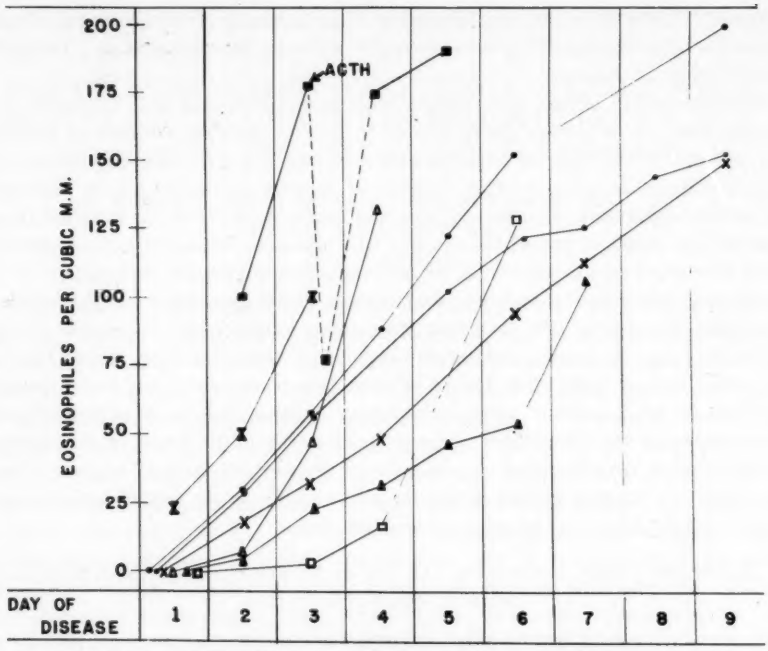


CHART 1. Eosinophil response of patients making uneventful recovery from meningococcic infection.

critically ill, and none showed symptoms suggestive of the Waterhouse-Friderichsen syndrome.

In sharp contrast is experience during the past year with three children whose blood eosinophil level on admission to the hospital was found to be little if any below the range for normal healthy children despite the fact that they were extremely ill with meningococcic infection. One of these patients showed definite evidence of shock, and died in little more than one hour after admission to the hospital. The second child showed every evidence of overwhelming infection and circulatory collapse and it was believed on admission that she would not survive. The condition of the third child was similar to that of the second but perhaps not quite so grave.

On clinical grounds the authors believe these children fell into the Waterhouse-Friderichsen category. Furthermore it was considered that the absence of eosinopenia demonstrated in each instance might be considered as evidence of poor adrenocortical response. For this reason all three patients were treated with cortisone in an attempt at replacement therapy. More detailed information regarding these patients is contained in the three case reports below.

CASE REPORTS

Case 1. K. A., a 5 mo. old male infant, was admitted to the hospital in a moribund state about 14 hr. after he had become ill. He had been noted to be feverish and irritable and had refused all feedings. Five hours prior to admission he was found to be pale and unresponsive. A physician was called who found a purpuric eruption and referred the infant to the hospital.

On examination the infant was found to be comatose and in a state of shock with cyanotic mottling of the extremities. Temperature was 39°C.; pulse 250/min.; respirations 50/min. Blood pressure was unobtainable. There were petechiae scattered over the trunk and extremities. The anterior fontanelle was soft and flat. Respirations were rapid and shallow but the lungs were clear and the heart sounds were of poor quality.

Laboratory data: The blood eosinophil count was 130/cmm. on admission and 110/cmm. 1 hr. later. Lumbar puncture was not performed because of the critical condition of the child. Blood culture was positive for Neisseria meningitidis, type II alpha.

Despite vigorous treatment the patient died little more than 1 hr. after admission to the hospital. During this period therapy consisted of intravenous administration of blood, 0.85% sodium chloride and 5% dextrose, penicillin, sodium sulfadiazine and 40 cc. aqueous adrenal cortical extract. Cortisone 5 mg. was administered intramuscularly shortly before death.

At autopsy there was no gross adrenal hemorrhage but histologic examination showed the following changes: The capillaries of the reticularis were most strikingly engorged and there was hemorrhage throughout this layer. While there was less engorgement in the fascicular zone, there were areas showing hemorrhage reaching the outer surface of the adrenal. The distribution of lipids was irregular in the fasciculata; there was conspicuous lipid deposited within the cells of the reticularis. On thin paraffin sections, many of the cells of the reticularis showed nuclear changes indicative of severe degeneration and even necrosis. In the fasciculata there was occasional pseudogland formation.

Case 2. M. F., an 8 yr. old girl of Puerto Rican origin, became ill 14 hr. before admission with fever, vomiting and generalized pains in the back and extremities. She became progressively more feverish and lethargic. Shortly before admission, an extensive hemorrhagic eruption was noted over the face and extremities.

On admission to the hospital the child was critically ill. She was disoriented and stuporous, and could be roused for short periods only. Her temperature was 40.6°C, pulse 160/min. and respirations 55/min. Blood pressure was 40/0 in the left arm and was unobtainable on the right. There were many purpuric lesions scattered over the entire skin surface and mucous membranes. There was severe acrocyanosis and cyanosis of the circumoral region. The mucous membranes of the nose and throat were moderately injected. The heart was not enlarged but the sounds were of poor quality and barely audible. The lungs were clear. The liver edge was palpable 1 cm. below the costal margin. There was moderate resistance to flexion of the neck; Kernig's sign was negative. There were no focal neurologic signs. It was apparent that her condition was poor and her survival in serious doubt.

Laboratory data: Examination of the blood on admission showed: Hgb. 12.5 gm./100 cc., WBC count 10.4 thousand/cmm. of which 46% were polymorphonuclear cells, 45% lymphocytes, 4% eosinophils and 5% monocytes. Three days after admission WBC count was 35.5 thousand/cmm. of which 82% were polymorphonuclear cells, 13% lymphocytes and 5% monocytes. On the day of entry into the hospital urine analysis showed the following: specific gravity 1.030, 2+ albumin, sugar negative; on microscopic examination a moderate number of granular casts and 1 to 3 WBC/hpf were found. The urine was found to be normal after the 1st 3 days in the hospital. Chemical examinations of the blood were carried out on 4 occasions with the following results:

Day of Illness	Urea N mg./100 cc.	Sugar mg./100 cc.	CO_2 Content mEq./l	Chlorides mEq./l	Serum proteins gm./100 cc.	Na mEq./l	K mEq./l
1	32	123	19.1	102		135	5
2	27	250	25.9	98	5.3		
4				102	6.4	146	6.6
5	15	120	23.6	104		132	6.1

Spinal fluid examined on admission contained 40 cells/cmm. (all polymorphonuclear); the protein concentration was 27 mg./100 cc. and the sugar content 40 mg./100 cc. A few gram-negative diplococci were seen on microscopic examination. Cultures of the spinal fluid, blood, nose and throat obtained on admission all yielded Neisseria meningitidis, type II alpha. Two blood cultures obtained 3 and 4 days later were sterile.

Electrocardiogram obtained on the day of admission was normal, but next day slight suppression of the ST segment in leads I, V-2 and V-4 was observed. This depression was more marked on the patient's fourth day in the hospital. On the ninth hospital day ECG was again normal.

Course: Treatment was instituted soon after admission with an intravenous infusion of 500 cc. plasma followed by 500 cc. blood. Sodium sulfadiazine was given intravenously in a dose of 50 mg./kg. body weight every 8 hr. Crystalline penicillin was administered intramuscularly, 200,000 units immediately and 100,000 units every 3 hr. Aqueous adrenocortical extract (Upjohn) 60 cc. were given intravenously. The patient was placed in an oxygen tent.

After 3 hr. of supportive therapy there was some improvement in the patient's condition. The pulse and heart sounds were of better quality and the blood pressure rose to 85/55 mm.Hg. There was some clearing of the sensorium. However, despite continued therapy, the child again became stuporous and showed evidence of being in shock. Many large ecchymotic lesions appeared over the trunk and extremities. The respirations were rapid, shallow and irregular. The heart sounds were of poor quality and gallop rhythm was heard. The blood pressure dropped to 60/0 mm.Hg and the peripheral pulses were barely palpable. She was incontinent of urine and stool. The blood eosinophil level at this time was 75/cmm.

Fourteen hours after admission, cortisone 100 mg. was given intramuscularly and 100 mg. orally. The latter dose was promptly vomited. Since there was no evidence of improvement 2 hr. later cortisone 100 mg. was administered intravenously. Two additional doses of cortisone 50 mg. were given intramuscularly thereafter at 8 hr. intervals. Adrenocorticotropic hormone (ACTH) was given intravenously at 21 hr. (25 mg.), 27 hr. (25 mg.) and 40 hr. (15 mg.) after admission. During the 1st 24 hr. a total of 2250 cc. fluid was given intravenously with a total content of 240 mEq. sodium. Thereafter no saline was administered intravenously.

The blood pressure began to rise toward normal between 24 and 36 hr. after admission, but the patient's condition remained desperate. The heart rate remained rapid with the sounds of poor quality and with persistent gallop rhythm. The respirations were rapid and irregular. There were dullness to percussion and moist rales at both lung bases. The liver edge was palpable 5 cm. below the costal margin. Chest RG at this time revealed haziness of the lower half of each lung and increased prominence of the vascular markings. The cardiac contours appeared enlarged. Cortisone and ACTH were discontinued and the patient was digitalized. However the signs of cardiac failure were progressive with marked dyspnea, pulmonary congestion and dependent edema. Mercuhydrin, 0.5 cc. every 8 hr., was then administered for 3 doses and an excellent diuresis occurred during the next 24 hr. period.

On the third hospital day the patient was much more alert and cooperative. Dyspnea abated although there were still moist basal rales. The blood pressure was maintained at a normal level. The heart sounds were still of poor quality but gallop rhythm had disappeared. Many of the ecchymotic and purpuric lesions had undergone superficial ulceration. There were extensive gangrenous areas over the left knee and forearm and the terminal phalanx of the right 5th digit.

Thereafter there was continued improvement in the patient's condition with gradual clearing of the pulmonary signs and other evidence of cardiac failure. There was a transitory episode of migratory polyarthralgia and swelling of both knees on the fifth hospital day. This responded well to treatment with aspirin.

Circulating eosinophil counts are noted on chart 2. An initial count made 12 hr. after intravenous administration of 60 cc. aqueous adrenal cortical extract was 75/cmm. Four hours after the institution of cortisone therapy the level fell to 20/cmm. and to zero 12 hr. later. The eosinophil count thereafter remained at zero until the fifth day in the hospital when there was a sharp rise to 230/cmm. associated with clinical evidence of convalescence.

The response of the circulating eosinophils following the administration of ACTH was assayed on the 8th, 13th and 22nd day after admission. The results of these tests are described below: on the eighth day following the administration of ACTH 15 mg. there was a fall from 215 to 137/cmm. after 4 hr., or a decrease of 36%. On the thirteenth day after ACTH 25 mg. there was a maximal fall of 40% after 4 hr., from 156 to 94/cmm. On the twenty-second day, there was a fall of 64% after 4 hr. and 82% after 6 hr. with an initial eosinophil count of 422/cmm. and subsequent counts of 153/cmm. and 75/cmm., respectively.

Convalescence was prolonged because of the sloughing of many of the ecchymotic areas and

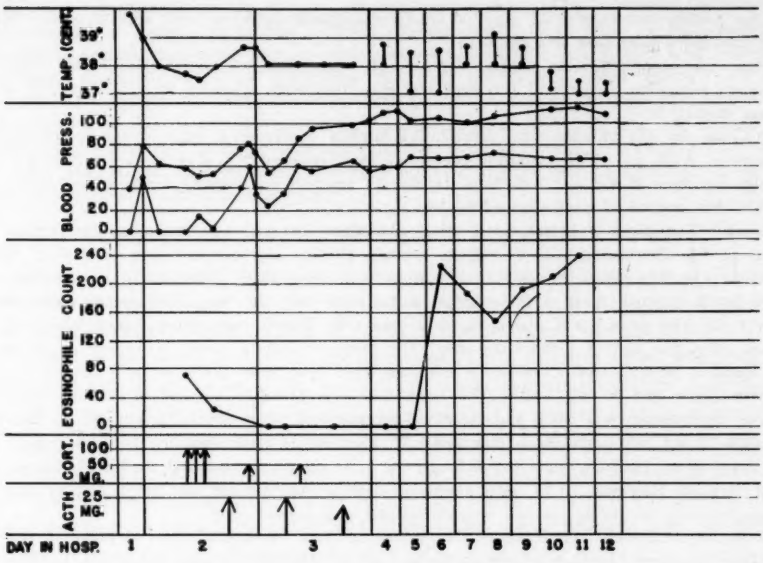


CHART 2. Case 2. Fulminating meningococcemia.

the healing of these lesions by granulation. The lesion over the left knee was particularly deep but healed without any contraction. The terminal phalanx of the right 5th digit became gangrenous but separation along the line of demarcation had not as yet occurred at the time of discharge to a convalescent home after 76 days of hospitalization.

Case 3. A. S., an 11 yr. old boy of Puerto Rican origin, was admitted to the hospital with a history of fever, headache and vomiting of 12 hr.' duration. His past history revealed no significant illness. The patient became ill about 12 hr. before admission when he returned from school and complained of headache and malaise. He vomited shortly thereafter and then fell asleep. One-half hour before admission his mother noted that he was feverish, unresponsive and that his skin was covered with spots.

Examination on admission to the hospital revealed the patient to be acutely ill and comatose. His temperature was 40.5°C., pulse 160/min. and respirations 40/min. Blood pressure was 80/40 mm.Hg. The skin was cold and mottled and there was acrocyanosis. Many purpuric spots and ecchymoses were present over the entire body. There were bilateral subconjunctival hemorrhages. The mucous membranes of the nose and throat were moderately injected and there were crusted secretions in the nares. The heart rate was rapid and the sounds were of fair quality. The lungs were clear. The liver and spleen were not enlarged. There was moderate stiffness of the neck and positive Kernig and Brudzinski signs. Deep reflexes were normal but the plantar reflexes were absent. Prognosis was grave.

Laboratory findings on admission were: Hgb. 12.0 gm./100 cc.; WBC count 18.8 thousand/cmm.; polymorphonuclear cells 89%, lymphocytes 9% and monocytes 2%. Blood urea nitrogen 24 mg./100 cc.; total serum protein 5.9 gm./100 cc.; plasma chloride 104 mEq./l.; sodium 128 mEq./l.; carbon dioxide content 23.0 mEq./l. On the day following admission, the plasma sodium was 142 mEq./l. and the potassium 5 mEq./l. Urine analyses during the 1st 3 days of hospitalization revealed 1 to 3 + albuminuria, occasional white blood cells and red blood cells and moderate numbers of hyaline casts. Subsequent urine specimens were normal.

Lumbar puncture on admission yielded cloudy spinal fluid under increased pressure. The fluid contained 1,300 WBC/cmm. of which 95% were polymorphonuclear. The sugar was 80 mg./100 cc.

and the protein content was 82 mg./100 cc. Gram-negative diplococci were seen on smear. Spinal fluid obtained 6 days later was normal.

Pure cultures of Neisseria meningitidis, type II, were isolated from blood and spinal fluid obtained on admission. Growth of this organism was completely inhibited by penicillin 0.02 u./cc. culture media.

ECG on the day of admission showed: RT slightly depressed in leads 2 and 3 and slightly elevated in AVR and AVF; multiple precordial leads revealed RT slightly elevated in V-2 and slightly depressed in V-3 and V-4. Next day the RT segment was slightly depressed in leads 1 and 2. ECG was normal 13 days after admission.

Course: Treatment instituted soon after admission consisted of continuous intravenous infusion of 5% dextrose in 0.85% sodium chloride solution and a transfusion of 250 cc. blood. Aqueous crystalline penicillin 500,000 u. was given intramuscularly immediately on admission followed by 100,000 u. every 3 hr.; sodium sulfadiazine 900 mg. was administered intravenously every 8 hr. The patient was placed in an oxygen tent. Despite supportive therapy the child remained stuporous and in a shocklike state. The blood eosinophil count performed on admission was found to be 130/cmm. Cortisone was administered 2 hr. after admission in a dose of 50 mg. intramuscularly and 50 mg. orally. The latter dose was promptly vomited. Two hours later no clinical improvement was noted and the blood pressure had fallen to 58/36 mm.Hg. At that time cortisone 50 mg. was administered intravenously. Eight hours after admission there was slight improvement in the patient's sensorium although the pulse remained weak and the blood pressure was 60/30 mm.Hg. However, 12 hr. after admission definite improvement was noted; acrocyanosis had disappeared and the blood pressure was maintained at a normal level.

Serial determinations were made of the circulating blood eosinophil count as noted in chart 3. The blood eosinophil count fell from an initial level of 130/cmm. to zero within 4½ hr. after the institution of therapy with cortisone and remained between zero and 15/cmm. during the next 4 days. Later in the convalescent period the eosinophil count rose to 75/cmm. on the sixth and 135/cmm. on the seventh hospital day. The course of the temperature and blood pressure are also noted on chart 3.

Cortisone 25 mg. were given by mouth twice daily on the second, third and fourth days in the hospital, and once daily for the next 3 days. Sulfadiazine and penicillin therapy were continued for a period of 8 days after admission.

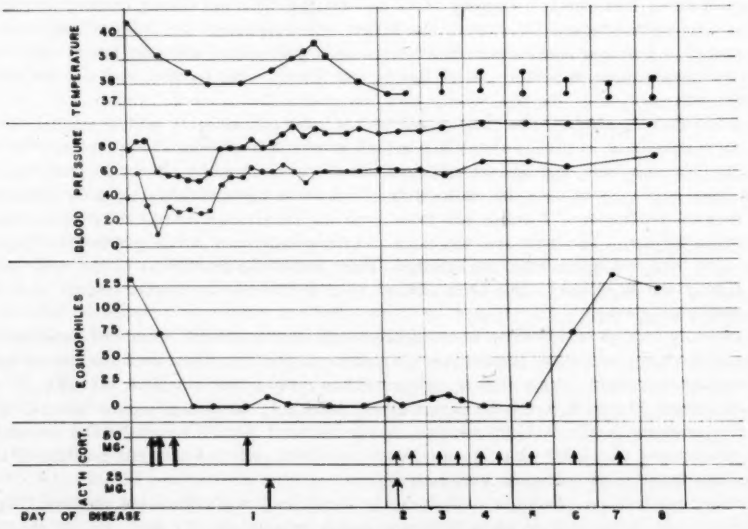


CHART 3. Case 3. Fulminating meningococcemia.

Progressive improvement of the patient's condition ensued with the temperature returning to normal after 24 hr. Signs of meningeal irritation subsided after 2 days. Many of the ecchymotic areas, which appeared during the first day of illness, became necrotic and formed large ulcerated craters which eventually healed by granulation. No other complications were observed and the child appeared to be entirely normal when discharged from the hospital 28 days after admission.

The response of the eosinophil count to the administration of ACTH 25 mg. was assayed on the thirteenth hospital day. There was a prompt fall from an initial level of 375/cmm. to 120/cmm. 2 hr. later. This fall in eosinophils representing a decrease of 68% may be considered to be an indication of normal adrenocortical function.

Discussion

The initial circulating eosinophil counts of 75 in Case 2 (after 60 cc. aqueous adrenal cortical extract) and 130/cmm. in Case 1 and Case 3 are in striking contrast with the uniformly low levels in the group of children who recovered without difficulty from mild to moderately serve meningococcus infections. These findings strongly suggest an inadequate response to severe stress, particularly when compared with the eosinopenia observed in the milder cases. Two possible theories may be evoked to account for this: (1) a deficient adrenocorticotrophic response to the increased peripheral utilization of corticosteroids which accompanies stress[14] or (2) a deficiency in adrenocortical function. Both Patients 2 and 3 were treated with ACTH and cortisone since it was deemed inadvisable to observe the effects of ACTH alone. The eosinophil response to ACTH was tested during the convalescent phase in both patients. Four hours after injection of ACTH Patient 2 exhibited a decrease in the eosinophil level of 36% when tested on the eighth day after onset of infection, and a fall of 40% on the thirteenth day. A decrease in the eosinophil count of 64% after administration of ACTH was obtained 22 days after the beginning of her illness. Patient 3 was similarly tested after 13 days and showed a drop of 68% two hours after ACTH. A fall of at least 50% in the circulating eosinophils is considered the lower level of normal response. It might be considered therefore that Patient 2 showed a decreased response to ACTH suggesting some impairment of adrenal function for over a week after the onset of illness. This conclusion must be tempered by the findings of Bonner and Homburger[15] who reported that several factors, including time of the day, nutritional status and the administration of salt and ascorbic acid, altered the responsiveness of the adrenal cortex as measured by the eosinophil count. They found that occasionally normal individuals exhibited a subnormal response with some lots of ACTH.

The disappointing or irregular response to treatment of the Waterhouse-Friderichsen syndrome with adrenal cortical extracts has been held as evidence against the existence of adrenal insufficiency in this condition. The ability of the organism to resist a variety of stress situations has been shown to depend upon the 11-oxygenated corticosteroids,[16–19] whereas desoxycorticosterone (with its major effect on salt and water) is ineffective. Patients with Addison's disease exhibit increased resistance to stress when treated with cortisone.[20] It should be noted that the doses of previously available adrenal cortical extracts that were recommended and employed for the treatment of fulminating meningococcemia were extremely low in cortisone-like activity. Typical doses of aqueous cortical extract advocated for children[10, 12, 13] ranged from 10 to 15 cc. administered initially followed by 3 to 10 cc. every 2 to 3 hours. One cc. of aqueous adrenal cortical extract contains the biologic activity of 0.1 mg. cortisone, while the lipoextract is about 10 to 20 times as potent. Thus the dose of cortisone employed in the treatment of the present patients

contained the equivalent of approximately four liters of aqueous adrenal extract.

The results of therapy of the case reported by Faloon et al.[5] afford further evidence of the relative inefficiency of aqueous adrenal cortical extract. The level of circulating eosinophils continued to rise despite the administration of 10 cc. every three hours and fell to levels consistent with an adequate response to stress only after almost two days of therapy with a dose of 30 cc. every hour. In contrast the eosinophil level of Patient 2 reported here fell from 75 to 20/cmm. after four hours and to zero when next tested after 13 hours. In Patient 3 the eosinophil count fell to zero 4½ hours after cortisone administration.

The dose of cortisone necessary for the treatment of fulminating meningococcemia has not as yet been determined. Therapy of the first patient included an initial dose of cortisone 100 mg. orally and intramuscularly. The oral medication was promptly vomited. One and one-half hours later, cortisone 100 mg. was given intravenously. An additional dose of 100 mg. was given during the ensuing 24 hours. This dosage may have been excessive for there was fluid retention and evidence of cardiac failure that responded to treatment with mercurial diuretics and digitalization. The presence of toxic myocarditis makes it difficult to define the part played by cortisone in the pathogenesis of the cardiac failure. Therapy of the second patient included an initial dose of 50 mg. orally and intramuscularly followed by 50 mg. intravenously two hours later. The oral dose was not retained. An additional 50 mg. was given orally and retained 12 hours after admission. Thereafter he received 50 mg. daily for four days followed by 25 mg. daily for two days. There was no untoward effect noted with this regimen. The total intake of saline and fluids is another consideration of the total plan of treatment that requires further study. With the use of cortisone it is likely that the large volumes of fluid and saline formerly advocated may not be necessary or advisable.

Since the completion of the above studies there have been two reports concerned with the use of cortisone in the treatment of the Waterhouse-Friderichsen syndrome. Nelson and Goldstein[21] have reported the cure of two patients: the first, an 11 year old boy, received a total dose of 112.5 mg. during the course of 18 hours and the second, a 28 year old woman, was given 100 mg. intramuscularly every six hours with a total dose of 500 mg. Newman[22] described the cure of a four year old girl who was given cortisone 150 mg. intravenously during the first six hours and then 25 mg. four times daily during the next three days. The level of the circulating blood eosinophils was not studied in these patients. The indications for the concomitant use of adrenocorticotropic hormone are not clear. It was employed in the attempt to stimulate any functioning adrenal tissue capable of response.

SUMMARY

The total blood eosinophil count has been studied as an indicator of the adequacy of the adrenocortical response to the stress of acute infection. Marked eosinopenia was found in seven children on the first or second day of acute meningococcal infection of mild or moderate severity and in 18 other patients with rubeola, pneumonia or diphtheria. During convalescence the number of eosinophils in the blood became normal. An eighth patient, who was admitted during the recovery stage of mild meningococcal infection, exhibited a normal count which decreased sharply after the administration of ACTH.

In three patients admitted with fulminating meningococcal infection, an initial eosinophil count of 75/cmm. was found in one and 130/cmm. in the other two. The eosinophil

count response to the administration of ACTH did not return to normal until the third week in Case 2. These findings lend support to the belief that adrenal cortical function may be impaired in patients with overwhelming meningococcal infection.

Cortisone was employed in addition to usual forms of therapy in the treatment of three children with fulminating meningococcemia. One patient died shortly after admission and the other two patients survived. It is believed that cortisone was of value in these latter two cases and that one of these patients would have certainly succumbed without its use. Cortisone may prove to be of value in the treatment of fulminating meningococcal infection because it is much more potent in overcoming stress than previously employed adrenal extracts. It is suggested that the circulating eosinophil count may be of value as a guide in the prognosis and treatment of meningococcal infections.

References

1. Lams, H., L'eosinophile considerée comme moyen de prognostic, Compt. rend. Soc. de biol. **62**:489, 1907.
2. Dalton, A. J., and Selye, H., Blood picture during alarm reaction, Folia haematol. **62**:397, 1939.
3. Thorn, G. W., Forsham, P. H., Prunty, F. T. G., and Hills, A. G., Response to pituitary adrenocorticotropic hormone as test of adrenal cortical insufficiency, J.A.M.A. **137**:1005, 1948.
4. Hain, K., Circulating eosinophils in children in health and disease, PEDIATRICS **7**:408, 1951.
5. Faloon, W. W., Reynolds, R. W., and Beebe, R. T., Use of direct eosinophil count in diagnosis and treatment of Waterhouse-Friderichsen syndrome, New England J. Med. **242**:441, 1950.
6. Williams, H., Meningococcal infections in infancy and childhood, M. J. Australia **2**:557, 1942.
7. Ferguson, J. H., and Chapman, O. D., Fulminating meningococcic infection and so-called Waterhouse-Friderichsen syndrome, Am. J. Path. **24**:763, 1948.
8. Rich, A. R., Peculiar type of adrenal cortical damage associated with acute infections, and its possible relation to circulatory collapse, Bull. Johns Hopkins Hosp. **74**:1, 1944.
9. Kinsman, J., D'Alonzo, C., and Russi, S., Fulminating meningococcic septicemia associated with adrenal lesions, Arch. Int. Med. **78**:139, 1946.
10. Smith, M. H. D., Waterhouse-Friderichsen syndrome: Its treatment with adrenal cortex extract, abstracted, Am. J. Dis. Child. **69**:330, 1945.
11. Strick, M. H., Fulminating meningococcemia, J. Pediat. **24**:675, 1944.
12. Ceballos, A., Frank, T. V., and Simpson, W. F., Waterhouse-Friderichsen syndrome, J. Pediat. **27**:281, 1945.
13. Wright, D. O., and Reppert, L. B., Fulminating meningococcemia: Report of four adult patients who recovered, Arch. Int. Med. **77**:143, 1946.
14. Roche, M., Forsham, P. H., Forsham, C. C., and Thorn, G. W., Study of adrenocortical response in health and disease: 48 hour ACTH test, J. Clin. Endocrinol. **10**:834, 1950.
15. Bonner, C. D., and Homburger, F., Some factors altering level of circulating eosinophils: Their significance in measurement of adrenal cortical responsiveness by eosinophil counts, Bull. New England M. Center **13**:187, 1951.
16. Sayers, G., and Sayers, M. A., Regulation of pituitary adrenocorticotropic activity during response of rat to acute stress, Endocrinology **40**:265, 1947.
17. Kendall, E. C., Glandular physiology and therapy: Function of adrenal cortex, J.A.M.A. **116**: 2394, 1941.
18. Ettelson, L. N., Inability of desoxycorticosterone acetate to protect adrenalectomized rats against typhoid vaccine, Endocrinology **27**:340, 1940.
19. Lewis, L. A., and Page, I. H., Studies on protective power of adrenal extract and steroids against bacterial toxins in adrenalectomized rats, Ann. New York Acad. Sc. **50**:547, 1949.
20. Thorn, G. W., and others, Advances in diagnosis and treatment of adrenal insufficiency, Am. J. Med. **10**:595, 1951.
21. Nelson, J., and Goldstein, N., Nature of Waterhouse-Friderichsen syndrome: Report of case with successful treatment with cortisone, J.A.M.A. **146**:1193, 1951.
22. Newman, L. R., Waterhouse-Friderichsen syndrome: Report of cure effected with cortisone, J.A.M.A. **146**:1229, 1951.

SPANISH ABSTRACT

Meningococcemia Fulminante Tratada con Cortisona: Uso de la Cuenta de Eosinófilos de la Sangre como Guía para el Pronóstico y Tratamiento

Existen varios estudios en adultos que permiten asegurar que la cuenta de eosinófilos de la sangre es un índice acceptable de la función adrenocortical. También en niños se ha demostrado, cuando la capacidad funcional potencial de sus glándulas suprarrenales es normal, que al sufrir una infección aguda desciende su cuenta total de eosinófilos en comparación con su cifra en estado de salud. En observaciones similares, los autores de este trabajo encontraron de 0 a 25 eosinófilos por milímetro cúbico en la determinación pre-admisión de un grupo de niños con sarampión, neumonía neumocóccica y difteria en contraste con cifras de 125 a 300 en niños normales.

Ya ha sido reportado que las cuentas seriadas de eosinófilos durante el tratamiento de un enfermo con meningitis meningocóccica que presentaba síntomas pertenecientes al síndrome de Waterhouse-Friderichsen fueron de valor, aceptando el nivel de eosinófilos en la sangre como un índice de la respuesta adrenocortical y de guía en la regulación de la terapeútica con extracto suprarrenal total.

Se ha demostrado, tanto por el cuadro clínico como por datos necrópsicos, hallados en casos de síndrome de Waterhouse-Friderichsen por meningococcemia, la existencia de cierta grado de insuficiencia suprarrenal aguda que juega un papel importante en su patogénesis sospechándose que ésta sea responsable de la alta mortalidad del padecimiento. Aunque en forma general se acepta que la hemorragia de la corteza suprarrenal es la causa íntima de la insuficiencia aguda de dicho síndrome, se han encontrado casos con ausencia de hemorragia franca al examen post-mortem y otros en que existe necrosis focal extensa pensándose que la susceptibilidad a los cambios degenerativos de la corteza suprarrenal pueda ser determinada o aumentada por la deplesión del material lipoide de las células corticales a consecuencia de un estado de "angustia" aguda. Estos conocimientos han hecho que se use el extracto suprarrenal total en el tratamiento de la meningococcemia fulminante pero la eficacia de esta terapéutica ha sida dudosa. Dado que en el niño con meningitis por meningococcemia los casos fatales están en gran parte limitados a aquellos que presentan síntomas de colapso circulatorio y shock, bien sea desde su entrada al hospital o después de un período de bienestar aparente, haciendo imposible, cuando menos para ciertos enfermos, hacer pronóstico alguno, los autores de este artículo pensaron que estimaciones repetidas de la función de la corteza suprarrenal por medio de la cuenta total de eosinófilos pudieran dar alguna información de valor para el pronóstico y consecuentemente para el tratamiento de este padecimiento permitiéndo reconocer los estados de insuficiencia adrenal antes del principio del cuadro clínico de colapso y prevenir tal eventualidad. Se supuso que una eosinofilia baja al principio de una infección meningocóccica indicaría una respuesta suprarrenal adecuada y, contrariamente, una cuenta de eosinófilos dentro de las cifras normales en presencia de una infección severa podría indicar una función suprarrenal inadecuada.

En 8 enfermos con sepsis meningocóccica o meningitis de severidad promedio, que nunca estuvieron en condición crítica ni presentaron signos de shock o cualquier otro sugestivo del síndrome de Waterhouse-Friderichsen, se encontró, en 6 de ellos, cero eosinófilos en su cuenta inicial. En el septimo caso había 25 y 100 en el octavo. Los 7 primeros alcanzaron sus valores normales entre el tercero y séptimo día después de iniciado el tratamiento y en el octavo enfermo, cuya cifra fué de 100, se comprobó que existía una reserva funcional suprarrenal adecuada y que estaba ya en convalescencia al hacer su cuenta de eosinófilos.

En contraste con este grupo de enfermos se presentan 3 casos cuyo nivel de eosinófilos al admitirse al Hospital fué normal o acaso ligeramente inferior al de niños sanos a pesar de que estaban seriamente enfermos de una infección meningocóccica. Uno de estos enfermos mostraba sintomas evidentes de shock y murió en la hora siguiente después de admitirlo; tenía 123 eosinófilos por milímetro cúbico y 110 una hora mas tarde, el hemocultivo aisló meningococo y en la autopsia se encontró congestión intensa y hemorragia de la zona reticular y cambios similares aunque mas ligeros en la zona fascicular. Microscópicamente las células de la zona reticular mostraban degeneración y aun necrosis. El segundo enfermo tenía síntomas de infección masiva y colapso circulatorio, su cuenta inicial de eosinófilos fué de 75 por milímetro cúbico, descendió a 20 cuatro horas después de iniciar su tratamiento con cortisona y a 0 en las 12 siguientes permaneciendo ausentes hasta el quinto día cuando subieron a 250 simultáneamente con el principio de su convalescencia. El tercer enfermo, quizas no tan grave como el anterior, tenía 130 eosinófilos a su entrada al hospital y bajaron a 0 a las cuatro y media horas

después de iniciada la cortisona permaneciendo entre 0 y 15 durante los cuatro días siguientes, subiendo a 135 cuando se inició la mejoría clínica a los 7 días después de admitido.

Se consideró que clínicamente los 3 casos caían dentro del síndrome de Waterhouse-Friderichsen y aun más, que la ausencia de eosinopenia podía ser considerada como una prueba de la pobre respuesta de sus glándulas cortico suprarrenales y por dicha rázon los 3 enfermos fueron tratados con cortisona como terapia de substitución. Los resultados obtenidos en los 2 últimos casos en que hubo tiempo de que ésta actuara sugieren un efecto benéfico del tratamiento y cuando menos por la prueba de la respuesta eosinofília al A.C.T.H. realizada durante el periódo de la convalescencia en los dos enfermos que curaron, es posible que haya existido en el segundo caso cierta disminución de la función adrenal que duró mas de una semana después del principio de su enfermedad. En el tercer enfermo, a juzgar por la ausencia de aumento de los 17 ketosteroides urinarios, respués del A.C.T.H., parece que también haya existido cierta disminución de la reserva funcional de las suprarrenales durante la fase aguda de su padecimiento.

La dosis total de cortisona empleada en el primer enfermo, que teniá 8 años de edad, fué de 300 miligramos en un período de 24 horas, y en el segundo, de 11 años de edad, se le administraron 150 mlgs. en las primeras 24 horas a partir de las cuales se continuó con 50 miligramos diarios por 4 dias y 25 por 2 días más. Es posible que en el primer enfermo la dosis haya sido excesiva ya que hubo retención de agua y síntomas de insuficiencia cardiaca siendo difícil de evaluar la participación de la cortisona en dicho cuadro pues existía simultáneamente una miocarditis tóxica.

El autor concluye que la adición de la cortisona al tratamiento usual fué de valor indudable en los dos casos que curaron y en vista de que es una forma mas potente de terapeútica de substitución que la de los extractos adrenales cree que se llegue a demostrar que la cortisona tenga su sitio definitivo en el tratamiento de la infección meningocóccica fulminante.

Después de terminar el estudio de estos enfermos, han aparecido en la literatura dos casos mas de curación de síndrome de Waterhouse-Friderichsen tratados con cortisona.

11 East 100th Street

FAT DISEASE OF THE LIVER IN INFANTS ON THE ISTHMUS OF PANAMA

By FRED H. HOWARD, M.D.,* AND WILLIAM A. MERIWETHER, M.D.
Ancon, Canal Zone

IN THE past few years a number of reports of a fatty liver disease in infants have appeared in the literature. Most of these reports have appeared in nonpediatric journals, and the syndrome, relatively unknown to the pediatrician, has been variously called kwashiorkor, malignant malnutrition, infantile pellagra, and fatty liver disease. Mitchell-Nelson's Textbook of Pediatrics[1] has devoted several paragraphs to this condition. Most recently this poorly understood syndrome was discussed at some length at the Conference of Joint Food and Agriculture Organization (FAO) with the World Health Organization (WHO)[2] in Rome, and its importance, especially in tropical areas, was reiterated and the need for further investigation stressed.

That report was the result of a recommendation made by the Joint FAO/WHO Expert Committee at its first session in Geneva in October 1949. The scope of the problem is well stated in the Committee's report:[3] "One of the most widespread nutritional disorders in the tropical and sub-tropical areas is a syndrome at present ill-defined, known by various names such as kwashiorkor, malignant malnutrition, polydeficiency disease, m'buaki, syndrome dépigmentation-oedème, infantile pellagra, etc. The committee is satisfied that this condition is not identical with classical pellagra, and suggests that the name (infantile pellagra) should not be used for this syndrome. It appears that the highest incidence of the disease occurs in infants and young children and that the mortality rates in some parts of Africa are disturbingly high. . . . There is considerable evidence to suggest that this syndrome is associated with the development of cirrhosis in many individuals who survive the acute forms of the disease. Cirrhosis of the liver in some form has been found in a significant number of adults in some parts of Africa and Central America, where kwashiorkor occurs in infants and children. The possible relationship of this cirrhosis to the development of primary carcinoma of the liver, a not uncommon condition in some of these areas, must also be recognized."

Over the past 10 years a number of infants either dead on arrival or dying shortly after admission have been seen at Gorgas Hospital where one common pathologic finding was noted—gross and microscopic fatty metamorphosis of the liver. The diagnosis was not made clinically in most cases, nor was it even suspected. Hence, essential laboratory studies were not done in most instances. However, the authors feel that it is important to summarize the clinical findings for comparison with the existing literature, and to present suggestions for further observation and study of these babies, particularly from the diagnostic and laboratory point of view. It will only be through early diagnosis that a complete understanding of the disease will be reached. One of

From the Pediatric Section and the Board of Health Laboratory, Gorgas Hospital, Ancon, Canal Zone.

(Received for publication Sept. 9, 1951.)

* Present address: 1430 Tulane Avenue, New Orleans.

the authors (F.H.H.) observed a case of cirrhosis of the liver in an infant from Honduras at Charity Hospital, New Orleans, in 1950, and at that time the paucity of information relative to the infant liver was vividly presented. This case may well have been the end result of a fatty liver in earlier infancy.

The purpose of this paper then is to summarize what information has accrued at this hospital over the past 10 years in cases of infants presenting fatty metamorphosis of the liver at autopsy, and from these data to outline a course for further investigation.

Review of the Literature

A fatty liver syndrome has been described in many tropical countries[4] including the African Gold Coast,[5] Uganda, South Africa, Basutoland, Costa Rica, Guatemala, Cuba, San Salvador, Malaya, Nigeria, Fiji Islands, and the British West Indies.[6,7] A comprehensive survey of the latter region was reported recently by Waterlow,[6] whose monograph includes a thorough review of the literature to that time. No attempt will be made to repeat that review and only a few of the milestones in the literature will be mentioned before presenting the present authors' data.

The first report of this fatty liver syndrome was that of Cecily Williams[8] in 1933, and she referred to the afflicted infants as "kwashiorkor" or "red boy" in the dialect of the Ashanti of the Gold Coast where she observed the disease. In addition to the fatty liver there were noted edema, cheilosis, diarrhea, vomiting, scant hair, irritability and raw reddish areas of skin with reddened mucous membranes. The skin was described as being desquamated in a unique fashion. The uniformly fatal outcome unless treated early and the nutritional basis were described at some length. Other observers[9,10] believed these skin lesions to be pellagrous in origin and the term infantile pellagra was applied. Trowell,[11,12] who introduced the term "malignant malnutrition," emphasized nutritional edema and pellagra as essentials of the syndrome, stating that the "crazy-pavement" dermatosis was also an essential diagnostic point. Waterlow[6] quotes Trowell as follows: "There occurs largely in tropical Africa and tropical America an acute and fatal disease which commonly attacks infants in the first few years of life. It is called by a different name in almost every country. It is frequently seen shortly after weaning. It is characterized by oedema, 'crazy-pavement' skin, diarrhea, cheilosis, and stomatitis, generalized pallor of the skin and pale, straight, scanty hair. Neurological changes may occur, but are slight and terminal. Microcytic or macrocytic anemia and steatorrhea are variable features."

In all cases presumptive evidence points to a multiple dietary deficiency in these infants, with the emphasis on low protein intake. The picture as reported from various sections of the world appears to be one and the same thing, a primary fatty metamorphosis of the liver, on a nutritional basis, with rather marked variation in the clinical pattern. Recently, fragmentation of the pancreatic parenchyma with cystic dilatation of the acini and cirrhosis have been reported.[6,13–15] Very little has been done biochemically with the disease other than to correlate low plasma protein levels and abnormal bromsulfalein tests.[6] This is not surprising in view of the fact that few of the authors' patients lived more than one day after reaching medical attention.

Waterlow's[6] work in Jamaica demands special note. He found that in the West Indies certain of the prominent features of the African cases were absent, namely, the skin and hair changes. That both the West Indian and African cases differed from ordinary malnutrition was emphasized, and the higher mortality, poorer response to therapy, and

the presence of fatty metamorphosis of the liver were offered as evidence. Because of the early demise of these infants when finally brought to the hospital, Waterlow went out into the native villages to find his cases, and reports on 15. The diets of these were poorly defined, but in general were high in carbohydrate and low in protein. Waterlow noted that the West Indian babies had a marked falling off in weight-gain on weaning, presumably on a nutritional basis. Presenting complaints in his series were edema and vomiting, but he did not find diarrhea. Other findings were weight loss, muscular wasting, large livers, mild glossitis, and angular stomatitis. A tendency to respiratory infections was noted. Either a normocytic or a macrocytic anemia was found in many cases. The values for total protein in the plasma were low, running 4.5 gm./100 cc. in 8 of 14 cases, the reduction being mainly in the albumin fraction. Bromsulfalein tests indicated impaired liver function, but the serum alkaline phosphatase values were normal. No evidence of hypochlorhydria was found. No relationship was found to lues, malaria, or other parasites. Liver biopsies were used to confirm his clinical diagnoses. The therapy which he found to be of greatest value was a high milk diet. Methionine, choline and inositol in a limited trial were of no value. He mentions the possible relationship of the cirrhotic liver to the deficiency state with fatty livers in infancy.

Although no satsfactory method of treatment can be deduced from the various papers, an adequate diet with sufficient milk protein is most helpful provided the disease has not progressed too far. Gillman and Gillman[16] report no improvement with methionine, but obtain favorable results[17] with 10 gm. daily of whole extract of hog stomach (ventriculin®) plus 10 cc. N/10 hydrochloric acid.

Gorgas Hospital Cases

Between 1941 and 1951 there were 48 cases of marked fatty metamorphosis of the liver in infants either dead on arrival or admitted to Gorgas Hospital, which came to autopsy. In this same period of time there were 5,714 autopsies (excluding stillbirths), making the incidence of fatty liver disease 0.8% in the postmortem series at the Board of Health Laboratory. Twenty-five of these patients were male and 23 were female. All the cases were in the native population, some of British West Indian Negro ancestry and others of mestizo or mixed race groups. Unfortunately very little information is available on many of the charts as 46% or 22 patients were dead on arrival and 32% lived less than 24 hours after admission. Nine survived from 1 to 7 days in the hospital and only 2 survived more than 1 wk. Their ages ranged from one to 17.5 months, with an average of 6.9.

Admission weights ranged from 2.5 to 10 kg. In terms of percentiles, based on the Harvard Nutritional Charts (which admittedly may be slightly high for babies in the tropics), 35 out of 48 or 73% were in the 3rd percentile, 2 were in the 10th, 2 in the 25th, 2 in the 50th, and 1 in the 75th. Thus, in spite of the clinical impression of well developed and well nourished babies, almost all were very small for their ages.

Symptoms: The presenting symptoms (table 1) were of considerable interest. Again, no reliable history could be obtained in many of the cases, especially those dead on arrival. Thirteen of the charts gave no history at all. Of the remaining 35 infants most were described as not particularly ill, but somewhat listless. Vomiting was present in 63%, and diarrhea, contrary to Waterlow's findings, was present in 51.5%. Fever was found in 31.5% of cases as an initial complaint; upper respiratory infections in 17%, with miscellaneous complaints as below.

Dietary History: Of the 48 cases reviewed here 30 had either no dietary history or a totally unreliable one. This was not entirely due to oversight by the physician, as many native parents do not know what or how much their children are eating, once weaned. An older sibling or a neighbor may have more to do with the feedings than the mother who works or is indisposed. Some parents would give the impression of actually trying to hide the facts of the dietary history. Cecily Williams[8] had a similar experience: "It often happens that a child is brought to the clinic, but the medical officer is not informed that the child is motherless. The fact may be simply ignored by the members

TABLE 1

PRESENTING SYMPTOMS: 35 CASES

	No. of Cases	Per Cent
Vomiting	22	63
Diarrhea	18	51.5
Fever	11	31.5
Colds	6	17
Feeding problems	6	17
Cough	3	8.6
Convulsions	2	6
Failure to urinate	2	6
Swelling of legs	1	3
Dermatitis	1	3

of a Coast tribe, or deliberately denied by an Ashanti. To obtain a family history a very patient investigation is necessary, questions having to be repeated in two, and sometimes three, languages. With many patients to be seen, it is sometimes only by good fortune that important points in a history are discovered." Seven of the infants at the Gorgas Hospital were fed entirely on klim®;* 2 had klim® plus soups, vegetables and eggs. Five were fed diets with definite multi-vitamin deficits. Three were breast-fed; one breast-fed plus supplemental evaporated milk-karo formula; 2 were on evaporated milk-karo formulas alone. Table 2 tabulates these findings. Further discussion of the dietary will be taken up in a later section.

TABLE 2

DIETARY HISTORIES

	No. of Cases
Unreliable or no report	30
Klim® alone	7
Klim® plus soups, eggs, etc.	2
Breast-fed	3
Breast plus EM-karo	1
EM plus karo alone	2
Barley water	1
Barley water plus condensed milk	1
No milk—1 mo. Pureed foods	1

Physical Findings: On admission most babies did not appear to be acutely ill. Many were listless. They seemed to be well nourished on superficial examination, but most were low in the percentile groupings. Fever over 37.8°C. per rectum was present in 13 of 28 recorded cases; edema was noted in 9 of 41 cases. Sparse hair was present in 10 of 33 cases, but how significant this might be is open to debate as many babies have "sparse hair" normally. "Crazy-pavement" skin was not seen in any cases, although one case did show some pigments changes. Cheilosis was found in 4 of 39 cases and glossitis in only one. The liver was felt to be more than 1.5 cm. below the costal margin in 18 cases, in some extending into the pelvis. Whether this represents in many patients a true enlargement of the liver is difficult to assess. Using tables[18] relating liver weight and age, 40% of the authors' patients were found to have a 15% or greater increase in liver size. However, using height-liver weight tables[18] 58% of the cases show an increase of similar magnitude. Muscular

* Powdered whole milk, Borden Co.

TABLE 3

PHYSICAL FINDINGS

	No. Cases	No. Reported	Per Cent
Below 3rd percentile in wt.	35	48	73
Liver down more than 1.5 cm.	18	34	53
Fever	13	28	46
Sparse thin hair	10	33	30
Muscular atrophy	7	31	23
Edema, generalized	9	41	22
Cheilosis	4	39	10
Glossitis	1	39	2.5

wasting was noted in only 7 cases; 26 definitely were not wasted and 15 were not reported. Table 3 summarizes the physical findings.

Laboratory Data: Very little information was obtained from the charts relative to laboratory data. This is not surprising when one considers that only 11 of the 48 patients were alive 24 hours after entering the hospital. Table 4 summarizes the sparse data, and but few conclusions can be drawn from this. The findings of 22 negative blood tests for syphilis and 3 positives, with no microscopic

TABLE 4

LABORATORY DATA

	No. Cases	Range	Average	
I. Hgb.	17	3.0–12.5	9.5 gm./100 cc.	
RBC	8	910,000	3,300,000	
		4,500,000		
WBC	9	6,000–16,600	10,570	
II. Urinalyses:	Cases			
Normal	5			
Pus	2			
Albumin	6			
NPN:		Average		
Antemortem	4	29.2		
Postmortem	11	79.0		
III. Cultures:	Negative	Positive		
Enteric	12	0		
Blood	1	1		
IV. Serologic Tests for Syphilis:				
Blood	15	2		
CSF	7	1		
V. Miscellaneous:	No. Cases	Values		
Cephalin flocculation	1	4+		
Bilirubin	1	4.17		
Total protein	3	5.5	Albumin	Globulin
		4.16	2.75	1.41
		4.9	2.96	1.94

evidence of lues in any of the autopsy findings, would seem to rule out lues as an etiologic agent. Likewise, no malaría organisms were seen in the blood smears and no other microscopic evidence of malaria was found.

Hemoglobin levels were surprisingly good, in 17 cases averaging 9.5 gm., with a range of 3.0 to 12.5 gm./100 cc. With exception of several low values, the levels were not below those seen in otherwise healthy Panamanian babies of similar age. RBC counts ranged from 0.9 million to 4.5 million/cmm. in 8 cases with an average of 3.3 million/cmm. No conclusions could be drawn as to the pattern of the anemia from so small a series.

The white cell counts were normal to moderately elevated except with severe dehydration. In 9 cases the range was 6 thousand to 16.6 thousand/cmm. with an average of 10.5 thousand/cmm. Differentials consistently showed a slight lymphocytic preponderance, a usual finding for this age group.

Stool cultures for enteric pathogens in 12 cases were negative. Blood cultures in 2 cases were negative, and in one case a pneumococcus, untyped, was grown.

Urinalyses were normal in 5 cases; pus cells were found in 2; and albumin was found in 6. Antemortem NPN in the blood of 4 cases ranged from 25.1 to 38.6 with an average of 29.2 mg./100 cc. In 11 cases postmortem NPN determinations averaged 79 mg./100 cc. This is probably indicative of a normal antemortem NPN in these cases.

Liver function studies were extremely rare, and apparently the possibility of liver disease was not considered in most cases. In one case a cephalin flocculation test of 4+ was found, a serum bilirubin of 4.17 mg./100 cc. and in 3 cases total plasma proteins were definitely low.

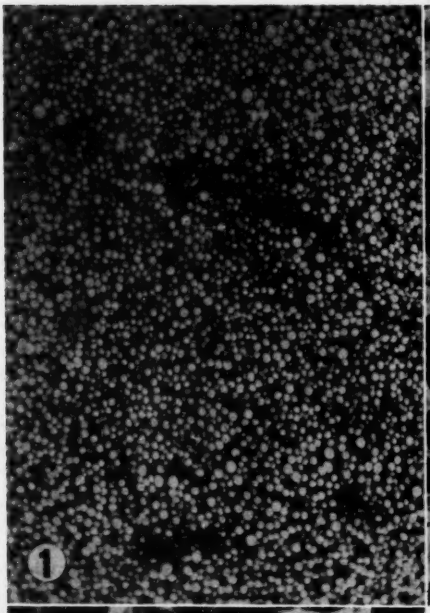
Course in the Hospital: Twenty-two of the 48 infants were dead on arrival and 15 lived less than 24 hr. In the latter group the babies did not appear particularly ill, although some were vomiting and feverish. Treatment was symptomatic, consisting of antibiotics, parenteral fluids, adequate diets, and oxygen. Transfusion of whole blood was given in several instances, and supplementary vitamins were administered in large doses to those surviving more than 24 hr. Ventriculin® was not tried.

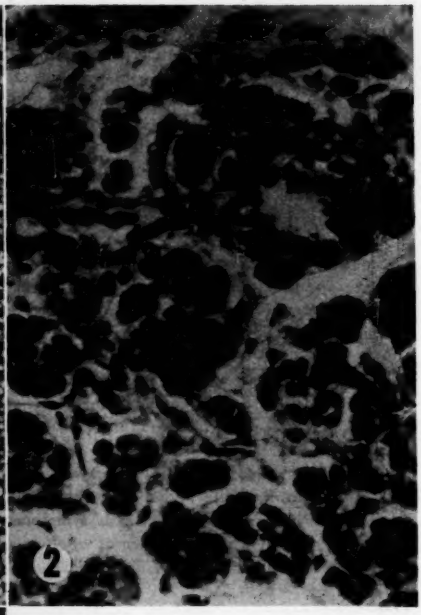
Case Histories

1. GH #168085, a 14.5 mo. old mestizo female admitted with chief complaint of diarrhea and vomiting for 5 wk. She had been fed exclusively on klim®, proportions unknown. She had received no supplemental vitamins or fruit juices. Physical examination: weight, 7.0 kg., placing her in the 3rd percentile; height, 72.5 cm; temperature, 37.5°C. per rectum; some muscular wasting; skin "tight" in spite of dehydration, with a variety of colors giving a mottled appearance—tan on arms to violaceous areas on abdomen to "white-ringed" areas on otherwise cyanotic feet; no edema; marked moniliasis of mouth without cheilosis; liver edge not felt; and sparse hair of normal texture. Laboratory data: Hgb. 12.1 gm./100 cc., WBC 7.7 thousand/cmm. with 39% polymorphonuclears and 60% lymphocytes; urinalysis—1+ albumin and 5 to 10 pus cells/hpf. Other studies were not done. She was given rehydration therapy, her temperature rose to 38.5°C. and in 48 hr. she suddenly died. Autopsy revealed the typical picture of fatty liver disease. Liver weight was 320 gm.

2. GH #619241, a 3.5 mo. old Negro female twin, whose sibling had died 1 wk. before of fatty liver disease after being fed exclusively on klim®, was admitted with the chief complaint of vomiting for 1 day only. She also had been fed exclusively on klim® since birth with no supplemental vitamins. Physical examination: temperature 37.5°C. per rectum; weight, 3.5 kg., placing her in the 3rd percentile; height, 48.7 cm.; robust appearance in spite of size; no edema or muscular wasting; normal hair and skin; no cheilosis or stomatitis; liver edge not felt. Laboratory data: Hgb. 10.2 gm./100 cc., RBC 3.2 million/cmm., WBC 13.2 thousand/cmm. with 67% polymorphonuclears and 33% lymphocytes, blood sugar 30 mg./100 cc. She lived 18 hr. after admission. Autopsy revealed fatty liver disease. Liver weight was 110 gm.

3. GH #608983, a 9 mo. old Negro female admitted with chief complaint of vomiting and diarrhea of unknown duration. No reliable dietary history could be obtained, indicating irregularity of meals. She appeared chronically ill. Physical examination: temperature 37.2°C per rectum; weight, 3.9 kg., placing her in the 3rd percentile; height, 55 cm., no edema, cheilosis or stomatitis; normal skin and hair; liver edge not palpable. Laboratory data: Hgb. 9.9 gm./100 cc., RBC 3.2 million/cmm., WBC 5.6 thousand/cmm. with 28% polymorphonuclears and 72% lymphocytes, tuberculin patch test negative, total plasma protein 4.9 gm./100 cc. with 2.96 albumin and 1.94





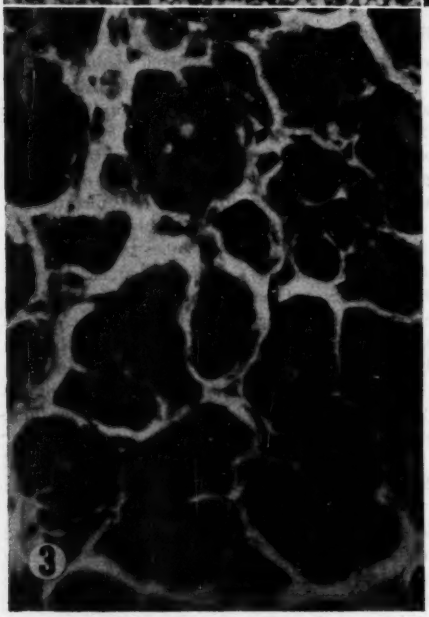


FIG. 1. Liver. Extensive fatty change in liver of malignant malnutrition. (x 55. Hematoxylin and eosin stain.) (Slides by R. G. Grocott; photomicrographs by H. A. Dunn.)

FIG. 2. Pancreas. Cytoplasmic atrophy and loss of normal acinar pattern in pancreas of malignant malnutrition. (X 238. Hematoxylin and eosin stain.)

FIG. 3. Pancreas. Normal pancreas for comparison with Fig. 2. (X 238. Hematoxylin and eosin stain.)

globulin. RGs of long bones and skull were normal. She was treated supportively with parenteral and enteral fluids and supplemental vitamins but died 8 days after admission. Fatty liver disease was found at autopsy. Liver weight was 290 gm.

4. GH #651360, a 1 mo. old mestizo male admitted with chief complaint of fever and vomiting for 3 days. He had had moderate diarrhea for 1 wk. and was described by his parents as "jittery." They had felt from his birth that he would not survive. He had been breast-fed exclusively and weighed 4.1 kg. His mother was in good health. Physical examination: temperature 37.0°C. per rectum; height, 55 cm.; marked facial edema; liver edge at umbilicus; straight fine and sparse hair; abdomen markedly distended; skin normal. Laboratory data: Hgb. 12.5 gm./100 cc. RBC 4.5 million/cmm., WBC 11.8 thousand/cmm. with 48% polymorphonuclears and 51% lymphocytes, slight sickle trait noted. Chest RG normal. Flat plate of abdomen interpreted as consistent with paralytic ileus. Lumbar puncture was done and the spinal fluid was entirely normal. Suddenly died after 24 hr. in the hospital. Typical fatty liver disease was found at autopsy. Liver weight was 160 gm.

5. GH #647634, a 14 mo. old mestizo male admitted with chief complaints of vomiting, diarrhea, fever and cough of 2 wk.' duration. No reliable dietary history was obtained. Physical examination: temperature 39.4°C. per rectum; weight 10.1 kg.; height, 62.5 cm.; acutely ill, lethargic, markedly dehydrated; liver enlarged; abnormal accumulations of fat on legs, buttocks and perineum; no edema, glossitis, or cheilosis; normal hair. Laboratory data: Hgb. 14.4 gm./100 cc., RBC 3.5 million/cmm., WBC 37.3 thousand/cmm. with 56% polymorphonuclears and 38% lymphocytes, 1 + albumin in urine, negative patch test. Shortly after admission a mass was noted in the groin and he passed bloody stools. It was felt that this should be investigated for a possible strangulated hernia, but a hydrocoele of the cord was found at operation. Chest RG revealed left lower lobe bronchopneumonia. He died 36 hr. after admission. In addition to the pneumonia and the operative wound, extensive fatty liver disease with cirrhosis was found. Liver weight was 400 gm. It is of some interest that his sister, aged 3 mo., had been brought in a terminal state to the hospital some months before. She had a markedly enlarged liver, extensive anasarca and fine scant hair. Autopsy revealed fatty liver disease with portal cirrhosis in this patient also.

Pathology

The 48 cases of fatty liver disease presented here were autopsied at the Board of Health Laboratory, Gorgas Hospital. The essential pathologic feature as found on the Isthmus of Panama is a fatty liver. At autopsy the infant, usually small but not emaciated, does not show cutaneous signs of deficiency diseases. The liver may be grossly recognized as fatty because of its pale yellow color and greasy feel on the cut surface. Microscopically the liver is striking. In its severest form the fatty change in the liver causes it to resemble adipose tissue. Each hepatic cell is distended by a droplet of fat which pushes the nucleus to one side, giving to the cell the appearance of a signet ring. The sinusoidal spaces are so compressed that they cannot be located. This picture was found in 30 of the 48 cases. The remaining 18 showed less severe fatty change in which a rim of cytoplasm of the hepatic cell could be made out around the fat, or the fat was distributed in several smaller vacuoles in the cell. The distribution of the fatty change in the liver lobule was for the most part general, with an occasional tendency to spare a few liver cells about the portal areas or about the central veins. Necrosis in the liver was not noted in any case. A periportal cellular infiltrate was noted in 13 of the 48 cases but in no instance was it severe. The cell type consisted mainly of mononuclears with an occasional polymorphonuclear leukocyte. Fibrosis of the liver was found in only 2 infants, siblings, who showed extensive portal cirrhosis associated with a fatty change in the remaining hepatic cells.

Pancreatic lesions have been described in the Jamaican series of fatty liver disease in infants as recorded by Waterlow,[8] in Africa by Davies,[15] in Fiji by Manson-Bahr,[13] and by Végheli et al.[14] in experimental animals fed diets deficient in protein.

Of the 48 cases in the present authors' series, 42 had slides of the pancreas available for study, and of these 15 showed microscopic lesions (Figs. 1-3). The changes consisted of a reduction in the amount of cytoplasm of the acinar cells, so that an acinus was represented by a practically bare cluster of nuclei. The impression gained is one of cellular atrophy with loss or blurring of the acinar pattern. This change does not resemble postmortem autolysis. One pancreas showed proliferation of the small ducts in an interlobular septum, and another showed dilatation of the acini in con-

junction with cytoplasmic atrophy. In no instance did fibrosis occur, and the islets of Langerhans showed no changes. Because of the finding of a significant pancreatic lesion in only 15 of the cases studied, the authors do not feel that the basic cause of this disease lies in the pancreas.

Discussion

That considerable variation exists in the clinical pattern of infants with fatty liver disease has already been mentioned. The Brock-Autret report[2] questions the use of the term "kwashiorkor" for the West Indies cases because of the failure of those infants to show skin changes. Since few show edema, the term "depigmentation-oedème" is likewise a poor one, and there is no evidence to substantiate the name "infantile pellagra." Hill's[7] concept of collagenosis seems reasonably clear, but one cannot be sure that this is not a variant or simply one stage in the natural history of fatty liver disease. The term malignant malnutrition has been loosely used but for want of a better term is justifiable. The present investigators believe the basic pathology common to all the series is the fatty liver and accordingly prefer the use of "fatty liver disease."

The diagnosis here is most difficult to make even within a few hours of death. Waterlow[6] has presented evidence using liver biopsies to show that severe liver damage may be present without dermatosis, glossitis, edema, or other signs. An enlarged liver may be of help, as will edema if present. While Waterlow found the bromsulfalein test helpful, in the authors' hospital practice none of the patients lived sufficiently long to undergo investigation. Indeed, Waterlow had to go out into the native villages to find early cases for his studies. The liver biopsy is the only final proof of the diagnosis before death.

The etiology of this disease is most certainly nutritional. Malaria, tropical parasites, antimalarial therapy, syphilis and liver changes secondary to other diseases have all been investigated and ruled out in the past, and upon summarizing the data from various papers from many tropical areas,[4,19] one reaches a common denominator—an inadequate protein intake. Forty-five of these infants were not breast-fed to any extent, and in the three who were nothing is known of the adequacy of the mother's diet. The type of protein consumed by the babies varied from one region to the next, although there was a large predominance of rice protein in the solid food group. Because of the great variation in the supplemental diets in various parts of the world, it will be surprising if deficiency of any single amino acid is found to be the causative factor. Similarly, in some cases there has been a deficiency of vitamin A clinically, in others of riboflavin, nicotinamide or thiamine. It is then a deficiency state, varying from one area to another with the type of diet available, and the amount. The clinical picture may be that of a "red boy" in the land of the Ashanti, of a badly wasted infant in Jamaica, or a small but healthy appearing infant in Panama.

The age incidence here in Panama is somewhat lower than that reported elsewhere. Williams[13] reported an average of 18 months on the Gold Coast and Waterlow found the cases in Jamaica to be some months older than the authors' average of 6.9 months. It is possible that weaning is accomplished at an earlier age in Panama, or more likely, that fewer mothers of the native population breast feed their infants for a safe length of time, taking their cue from the North American mothers of the Canal Zone who largely feed their babies artificially, or weaning the infant early in order to return to work. The difference between North Americans and natives would seem to be the inability of the natives to buy adequate diets for the babies and the lack of understand-

ing of what the baby needs for adequate growth, as the "local rate" (West Indian) worker has a large family to feed and rarely earns even one hundred dollars per month.

The prognosis is universally poor in the cases reaching the hospital in the authors' experience, as they already have progressed to an apparently irreversible state. How many infants with early fatty metamorphosis of the liver are seen by practising physicians and the diagnosis overlooked will never be known. Certainly one sees more cirrhosis of the liver in children in the tropics than in temperate zones[4, 6] and this leads to the speculation that the possible cause lies in the development of a fatty liver in infancy with subsequent cirrhosis. The cause of death in fatty liver disease appears to be hepatic failure with transient periods of coma or extreme listlessness. Death is remarkably sudden and unexpected, and frequently occurred in these cases in the arms of the startled parents on the way to the hospital, when they had just realized the seriousness of the child's condition. Waterlow found his infants particularly susceptible to respiratory infections, but this was not the case in Panama.

No conclusions could be reached as to the laboratory data, so sparse were the reports. The hemoglobin values were not unusually low, with few exceptions, for the average infant seen here. Nothing can be said as to treatment.

As to future investigations, it will very likely be necessary to follow Waterlow's method of going into the native villages to seek out the early cases and to study and treat them when hospitalized at that early stage. There are undoubtedly many such cases in Panama and other Central American countries. Studies should be directed at dietary surveys of the families from which actual cases are taken, and can best be accomplished by trained dieticians and physicians. Laboratory studies should be directed at both the liver and the pancreas, and actual metabolic balance studies should be conducted to get some idea of the ability of the bowel to absorb foodstuffs. Such surveys will necessarily be expensive. Therapy, however, can only be evaluated once the basic pattern is established. Blood levels of the various vitamins and vitamin absorption tests should likewise be studied.

Prophylaxis is another problem, and will involve a complete dietary survey of the region involved plus a survey of the economic status of the families. Here in Panama it has been estimated that the native populations outside the city areas may subsist on as little as $14 per month in addition to what local food products they may gather. The native in the Canal Zone does somewhat better, making from $40 to $100 per month. Milk is relatively expensive. Eggs, meats and wheat cereals are likewise beyond the financial possibilities of many of these natives. Along the coastal areas some fish may be used to supplement the diet. Rice, plantains, bananas, cassavas, citrus fruits, and some fresh leafy vegetables form the bulk of the diet. Once a baby is weaned, the possibilities of an adequate milk intake are slim. Some days the mother may conscientiously furnish an adequate supply, but more than often, the feeding is dependent on the available finances of the family. Klim® is the most popular whole milk substitute here, largely because of the refrigeration problem. Most mothers cannot tell the doctor how they mix the klim® and even when they do read the instructions will try to "stretch" the supply by adding excessive water. Another point of interest is the method of making meat soups. Once the soup is made, the soup bone is taken out and dried to be used again in similar fashion a number of times. Bush teas are often substituted for milk especially during periods of diarrhea. These teas are a conglomeration of herbs stewed in water

and are by no means a milk substitute. However, once the diarrhea is under control, the mothers feel that the tea has been so good that the baby is given a part of his daily diet in this form.

That some relationship may exist between fatty liver disease in infants and cirrhosis of the liver has been suggested by a number of observers. The authors have found five cases of cirrhosis in children under the age of 14 years that came to autopsy in the past 10 years. One that was definitely associated with a nutritional problem died at the age of 6 years weighing only 4 kg. and measuring 75 cm. in length. She had been admitted to the hospital at one year of age weighing 3.8 kg., with anorexia and vomiting of six months' duration, glossitis and a red, peeling, mottled skin. When next seen she was dead on arrival at the hospital, at the age of 6 years.

The possibility of carcinoma of the liver developing on the basis of a previously existing fatty liver has been mentioned in the literature,[6] but there is at present no evidence for or against it from these observations at Gorgas Hospital.

Fatty liver disease has so far been reported only from tropical or subtropical areas where large groups of people are on inadequate diets. If the basis is nutritional, then it should not be limited to tropical areas, but should appear wherever there is malnutrition. Therefore, the possibility exists that it has been overlooked, at least in isolated instances, in parts of the world other than the tropics, even in the continental United States.

Summary

Forty-eight cases of fatty liver disease in infancy coming to autopsy over the past 10 years at Gorgas Hospital are reported. The diagnosis of this condition is extremely difficult clinically; liver biopsy is the only certain way of making the premortem diagnosis. In Panama, vomiting, diarrhea and fever are the most frequent presenting complaints. Physical findings of help are the stunted growth, fever, and possibly enlarged liver. Other findings seen commonly in the African cases, such as edema, glossitis and dermatosis, are usually not seen. The essential pathologic finding is a markedly fatty liver. Pancreatic changes consisting of acinar atrophy were seen in some cases. The cause of the deficiency state appears to be an inadequate protein intake, and will not be simple to deal with, as poverty and ignorance, rather than neglect, would seem to be responsible for this disease. The prognosis is extremely poor, only 11 of the 48 patients surviving for more than 24 hours after medical attention was sought. It is probable that fatty liver disease in infants is relatively common in Panama but almost completely overlooked clinically.

Acknowledgment

The authors wish to acknowledge the assistance of Dr. Norman W. Elton, Chief, Board of Health Laboratory, Gorgas Hospital, in the preparation of this paper.

References

1. Mitchell-Nelson Textbook of Pediatrics, ed. 5, edited by W. E. Nelson, Philadelphia, W. B. Saunders Company, 1950, p. 879.
2. Brock, J. F., and Autret, M., Kwashiorkor survey in Africa, Draft Report for the Joint FAO /WHO Expert Committee on Nutrition, Rome, Italy, 1951.
3. Report of Joint FAO/WHO Expert Committee on Nutrition, Geneva, Switzerland, 1949.
4. Manson-Bahr, P., Manson's Tropical Diseases, ed. 13, Baltimore, Williams & Wilkins Company, 1950.
5. Davies, J. N. P., Kwashiorkor, in Liver Injury, Transactions of the Ninth Conference, edited by F. W. Hoffbauer, New York, Josiah Macy, Jr., Foundation, 1950.

6. Waterlow, J. C., Fatty Liver Disease in Infants in British West Indies, London, His Majesty's Stationery Office, 1948.
7. Hill, K. R., Liver disease in Jamaican children, in Liver Injury, Transactions of the Tenth Conference, edited by F. W. Hoffbauer, New York, Josiah Macy, Jr., Foundation, 1951, p. 263.
8. Williams, Cecily D., Nutritional disease of childhood associated with maize diet, Arch. Dis. Childhood **8**:423, 1933.
9. Trowell, H. C., Infantile pellagra, Tr. Roy. Soc. Trop. Med. & Hyg. **33**:389, 1940.
10. Trowell, H. C., Note on infantile pellagra, Tr. Roy. Soc. Trop. Med. & Hyg. **25**:13, 1941.
11. Trowell, H. C., and Muwazi, E. M. K., Severe and prolonged underfeeding in African children, Arch. Dis. Childhood **20**:110, 1945.
12. Trowell, H. C., Malnutrition in Africans as indication of their dietary requirements, East African M. J. **23**:34, 1946.
13. Manson-Bahr, P. E. C., Malignant malnutrition in Fiji, Tr. Roy. Soc. Trop. Med. & Hyg. **44**:555, 1951.
14. Véghelyi, P. V., Kemény, T. T., Pozsonyi, J., and Sós, J., Dietary lesions of pancreas, Am. J. Dis. Child. **79**:658, 1950.
15. Davies, J. N. P., Essential pathology of Kwashiorkor, Lancet **1**:317, 1948.
16. Gillman, T., and Gillman, J., Methionine and fatty liver of infant pellagrins, Nature **155**:634, 1945.
17. Gillman, T., and Gillman, J., Substitution of whole stomach extract for vitamins in treatment of malignant infantile pellagra, Nature **154**:210, 1944.
18. Coppoletta, J. M., and Wolbach, S. B., Body length and organ weights of infants and children, Am. J. Path. **9**:55, 1933.
19. Gillman, J., and Gillman, T., Perspectives in Human Malnutrition, New York, Grune & Stratton, 1951.

SPANISH ABSTRACT

La Enfermedad del Hígado Grasoso en Infantes en el Istmo de Panamá

Este artículo se refiere a cuarenta y ocho casos de la enfermedad del hígado grasoso en infantes cuyas autopsias han sido hechas en el Hospital Gorgas en los últimos diez años. El diagnóstico clínico de la enfermedad del hígado grasoso es extremadamente difícil ya que las biopsias del hígado es la única manera de hacer el diagnóstico premortem. En Panamá los primeros síntomas que se presentan son vómitos, diarrea y fiebre. Como signos físicos que ayudan al diagnóstico están la inhabilidad de crecimiento, la fiebre y el agrandamiento del hígado. Otros signos comunes sobre todo en los casos del Africa son edema, glositis, y dermatosis signos que no se encuentran en Panamá. El signo patológico esencial es el hígado grasoso. Cambios pancréaticos encontrados en algunos casos consisten en atrofiamento de los elementos glandulares. La causa de esta enfermedad parece ser la deficiencia de proteinas ingeridas. Este problema no es muy fácil de resolver debido a la pobreza e ignorancia de las clases trabajadoras que son las más afectadas por esta enfermedad y no por el descuido o abandono do proveer para sus hijos una dieta mejor balanceada. El pronóstico es extremadamente pobre; solamente 11 casos de los 48 sobrevivencia después de estar bajo atención médica por más de 24 horas. Es muy probable que la enfermedad de hígado grasoso en infantes sea muy común en Panamá pero no es reconocida clínicamente.

Gorgas Hospital

GUMMA OF THE STOMACH IN CONGENITAL SYPHILIS

By GEORGE WILLEFORD, M.D.,* JOHN H. CHILDERS, M.D., AND W. R. HEPNER, JR., M.D.
Galveston, Texas

GUMMA of the stomach is a rare manifestation of congenital syphilis. Voigt[1] in 1940 reported a case confirmed by pathologic studies. Jeans and Cooke[2] stated in 1930 that they had never been able to establish the diagnosis of syphilis tarda of the alimentary tract in the pediatric age group. It is the purpose of this presentation to point out that although the condition is rare, surgery and/or anti-luetic therapy can alleviate the symptomatology.

CASE REPORT

J.W.R., an 11 yr. old white male, was admitted to the University of Texas Children's Hospital with the chief complaint of intermittent bouts of vomiting for the previous 16 mo. The vomiting usually occurred from 15 min. to 4 hr. postprandially; the vomitus consisted of partially digested food. In addition, the patient suffered a severe intermittent nonradiating aching pain in the left upper quadrant of the abdomen. There had been periods of spontaneous freedom from the above complaints for 2 to 3 wk. at a time. During the previous 2 yr. he had lost 13.6 kg. The child's mother had a positive serologic test for syphilis. Otherwise the history was noncontributory.

Physical examination revealed a malnourished, chronically ill boy who looked older than his stated age of 11 yr. BP was 104/74 mm. Hg.; temperature 37.2° C. (R); P 80/min.; R 24/min.; weight 22.2 kg. (less than 3 percentile for age group); and height 137 cm. (less than 25 percentile for age group). The physical examination otherwise revealed no significant abnormalities.

Laboratory: RBC count 4.06 million/cmm.; Hgb. 14 gm./100 cc.; WBC count 7.6 thousand/cmm. with a normal differential cell count. Urinalysis was negative. Serum Na, 145 mEq./l.; K,4.5 mEq./l.; and Cl, 100 mEq./l. The Kahn test was positive and the Kolmer was positive in 1:320 dilution. The total serum proteins were 6.3 gm./100 cc. with a normal A/G ratio. Spinal fluid examinations (serologic test for syphilis, Lange curve, sugar, protein and cell count) were entirely normal. Many stools were examined for ova and parasites and all were negative. Erythrocyte sedimentation rate was 7 mm./hr. corrected (Wintrobe). Schick test was negative; O.T. skin test was negative 1:1,000. Three gastric analyses were made which revealed no free acid and no acid was present after histamine (1 mg.) was injected. Fluid from the stomach washings was fixed and stained for microscopic examination. Only lymphocytes, neutrophils and epithelial cells were found. Endoscopy through a straight esophagoscope revealed a red, friable, granular lesion on the greater curvature of the stomach. When the biopsy specimen was obtained, the resistance offered by the affected tissue was less than that usually expected. Histologic examination revealed chronic inflammation with no evidence of malignancy.

Barium enema and chest RGs were reported as entirely normal. Fluoroscopic study of the stomach showed a constant narrowing of the antral region, and films revealed a "niche-like" deformity in the greater curvature of the middle third of the stomach. Peristaltic waves were absent in this area. RGs of the long bones and wrists showed no evidence of heavy metal deposition or of other abnormalities.

A therapeutic trial consisting of procaine penicillin, 300,000 units every 12 hr., and potassium iodide (saturated solution) 5 drops daily was instituted for 14 days. At the end of this time, gastric fluoroscopy was repeated and the deformity of the stomach, previously detected, was not appreciably changed. Since the lesion was still present 1 mo. later, surgical exploration was carried out (Dr.

From the Departments of Pediatrics and Pathology, University of Texas Medical Branch, Galveston, Texas.

(Received for publication Feb. 10, 1952.)

* Present address: Harlingen, Texas.

FIG. 1. A. A-P view of original GI series showing filling defect of inferior ⅓ of stomach, also absent rugal markings. B. Right oblique view of above showing filling defect.

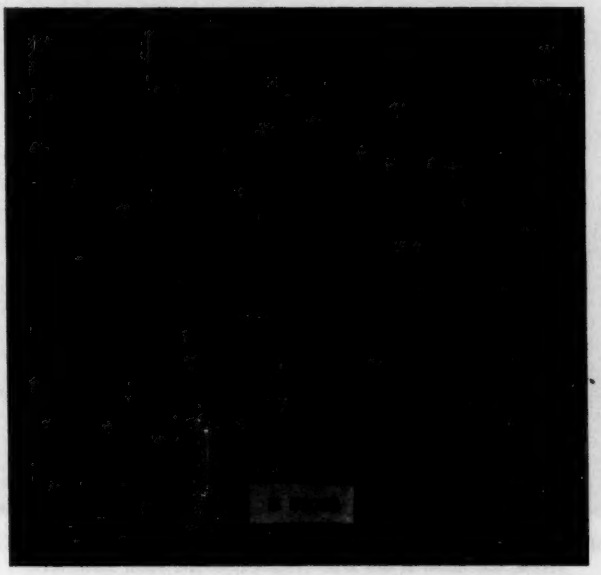


FIG. 2. Resected portion of stomach opened along greater curvature.

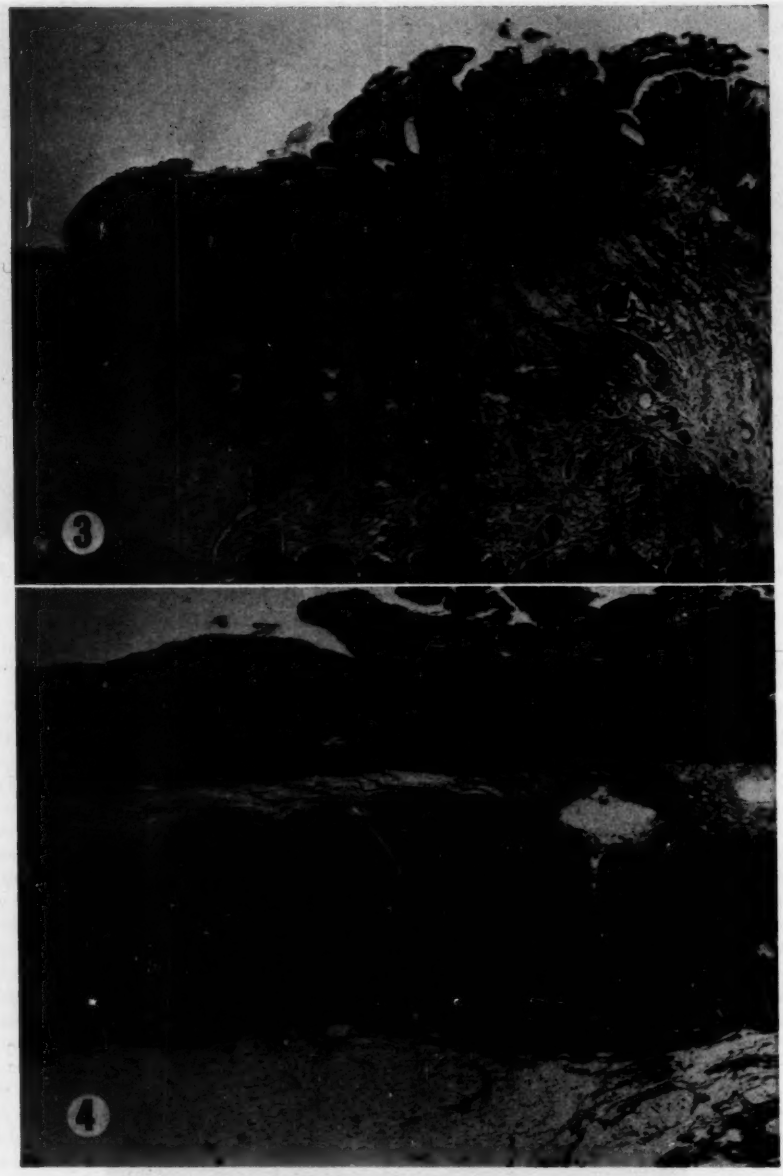


FIG. 3. Margin of ulceration with uniform adjacent mucosa. Small thrombus in submucosal vessels was noted at this area. Hematoxylin and eosin stain. X10.

FIG. 4. Hypertrophy of muscularis was marked. Abrupt termination of mucosa at ulceration was characteristic. Hematoxylin and eosin stain. X10.

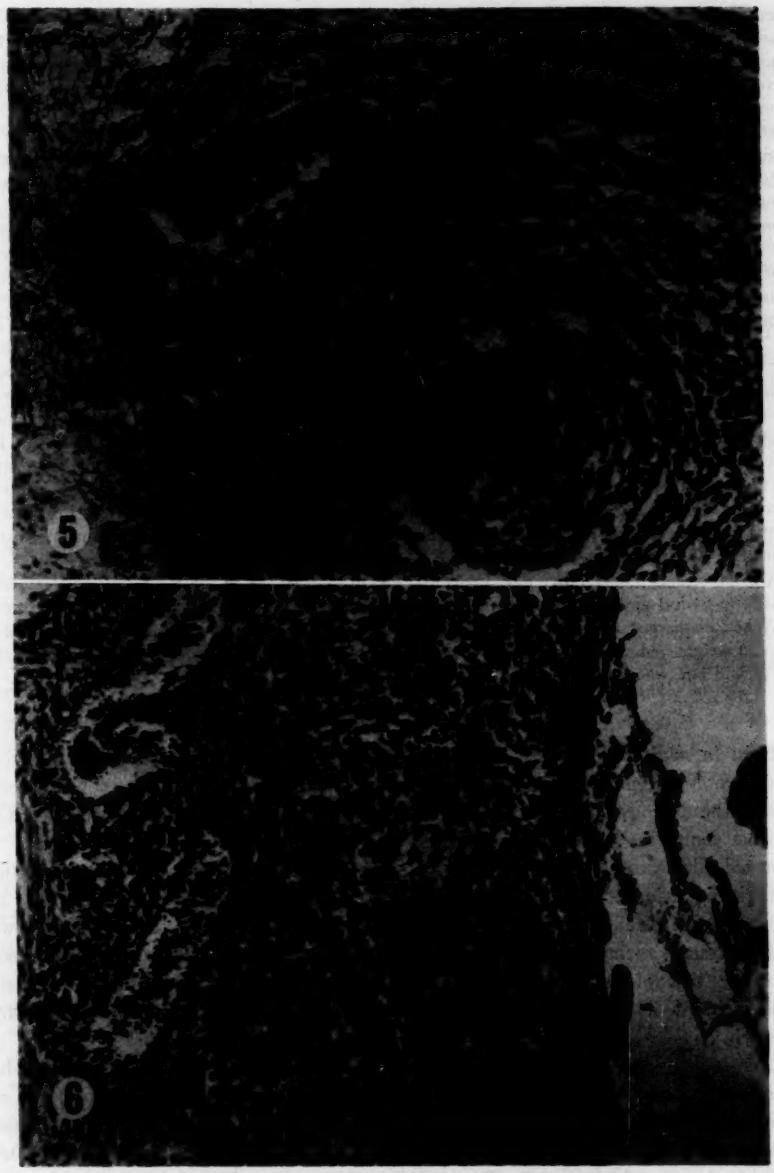


FIG. 5. Perivascular collection of inflammatory cells in submucosa. Majority of these cells were lymphocytes. Hematoxylin and eosin stain. X150.

FIG. 6. Base of ulcerated area showing many small vessels and dense inflammatory infiltrate. Hematoxylin and eosin stain. X150.

Fred Wolma). Two-thirds of the stomach was removed. The report from the pathologist (JHC) was as follows: "The resected segment of the stomach measured 12 cm. along the lesser curvature and 17 cm. along the greater curvature (Figure 2). The serosa was smooth, shiny and glistening. Several small, soft, grayish-pink, discrete lymph nodes were palpated in the yellow adipose tissue along the greater curvature. The stomach in the prepyloric region was rubbery in consistency. Sections through this area revealed an annular ulceration of the mucosa. The shaggy edges of this irregularly shaped ulcer were poorly defined. The distal portion of the ulcer was 3 cm. from the pylorus on the lesser curvature and extended 4 cm. along the wall. Two cm. of mucosa on the greater curvature were involved. The base of the ulcer was firm, pinkish-gray in color, and 1 to 2 mm. below the level of the surrounding mucosa. At the proximal margin of the resected specimen the rugae were broad and had a smooth mucosal surface. Sections perpendicular to the mucosal surface showed the submucosa to vary from 7 to 10 mm. in thickness. In the prepyloric region the muscularis layer measured 5 mm. in thickness, while in the proximal portion the muscularis was 3 mm. in thickness.

"Histologic study of 10 blocks of tissue, taken from various areas in the stomach, revealed a chronic inflammation with ulceration of the mucosa (Figs. 3-6). Numerous thin-walled vascular channels were present in the base of the ulcerated area (Fig. 6). In these same areas there was a dense infiltration of the mucosa and surrounding edematous connective tissue by lymphocytes, mononuclear cells and plasma cells. These inflammatory cells were more compactly arranged in the perivascular tissue. No areas of necrosis were encountered. All of the sections taken through the margins of the ulcerative lesion revealed uniform columnar epithelial cells forming acinar spaces in the mucosa (Fig. 3). An extensive reactive hyperplasia of the reticulo-endothelial cells of the sinusoids of the lymph nodes was noted. Masson's trichrome stains added no additional significant information. Spirochetes were not demonstrated with the Warthin-Starry stain."

On the second postoperative day, interstitial keratitis developed in the right eye. This responded readily to topical applications of cortisone.

When discharged from the hospital 3 wk. postoperatively, he had gained 4.1 kg. over the admission weight. Subsequent outpatient visits 6 wk. and 12 wk. later revealed a healthy, symptom-free 12 yr. old boy who was enjoying a normal home and school life.

Discussion

Even in adult subjects the clinical diagnosis of gumma of the stomach is difficult. Roentgenologic study, gastric analysis and specific therapeutic trial are employed in establishing the diagnosis. Specific serologic tests may be of significance in a patient with the chronic complaint of loss of weight, vomiting and abdominal pain. In many of the reported adult cases,[3-5] roentgenographic examination has shown a concentric, partially constricting lesion of the antrum and body of the stomach. The child reported here had this type of deformity. Syphilis of the stomach may manifest itself in several different ways and, of course, roentgenographic changes depend upon the type of involvement. Among these are: multiple ulcers, single ulcer, diffuse gummatous infiltration, nodular-ulcerative lesion, chronic-interstitial fibrosis, nodule, and linitis plastica or classical "water bottle" stomach.[3]

Gastric anacidity is rare during childhood, perhaps because disease processes which notoriously produce it (e.g., carcinoma of the stomach and pernicious anemia) are rare in children. When a histamine injection fails to produce gastric acid, luetic involvement as a possible etiology may well be entertained. Behrendt[6] feels that gastric analysis has a limited place in the pediatric diagnostic armamentarium. However, if luetic gastritis or a luetic solitary lesion is suspected, this test may be employed.

A favorable therapeutic response to antisyphilitic therapy may not, in itself, be regarded as proof of the syphilitic nature of a gastric lesion. Rafsky et al.[4] have pointed out that nonsyphilitic lesions may not heal until the associated syphilis is treated. The

present authors' patient's gastric lesion was not appreciably affected by an adequate course of penicillin and iodide therapy. It may be conjectured that if more time had been allowed to elapse after the completion of the course of therapy, an appreciable effect might have become apparent. However, Rafsky et al.[4] did not find evidence of complete healing six months after commencement of arsenic therapy. One might believe that if a particular gastric lesion responded to antiluetic therapy, this response would support diagnosis. Nevertheless, if there had been no response, late syphilis as an etiologic agent could not be ruled out. With the changing concepts of the nature of adequacy of early syphilitic therapy, it may be that when our knowledge is more complete we will be able to use the therapeutic test as an aid to diagnosis. If there is any question that syphilis is causative, therapeutic trial should be initiated.

The gastroscopic appearance of syphilis of the stomach has been described[4] for adults, but no reports on the appearance of this lesion in pediatric patients have been found.

Treponema pallidum is present only in small numbers in late congenital syphilis; hence the organisms are difficult to demonstrate histologically. Palmer et al.[7] have pointed out that failure to demonstrate the spirochete in biopsy specimens certainly cannot mitigate against an etiologic diagnosis of syphilis.

Summary

A gummatous lesion of the stomach due to congenital syphilis in an 11 year old white male is described.

A history of vomiting, chronic intermittent abdominal pain, and loss of weight in a child with a positive serologic test for syphilis suggested the possibility of gastric syphilis. The roentgenologic demonstration of a constricting lesion of the stomach, gastric anacidity, and gastroscopic visualization of a red, friable, granular lesion, with ulceration, suggests a syphilitic gastric lesion. Failure to "melt" the lesion with a therapeutic trial of antiluetic medication prompted surgical resection of a large portion of the stomach. A lesion, compatible with the diagnosis of gumma of the stomach, was found in the gross and microscopic examination of the removed tissue.

Acknowledgment

The authors are grateful to Dr. Arild E. Hansen, Chairman, Department of Pediatrics, University of Texas Medical Branch, Galveston, Texas, for his review of this manuscript.

References

1. Voigt, H. W., Stenosierende Magensyphilis bie einer Jugendlichen mit kongenitalen Lues, Deutsche Ztschr. f. Chir. **254**:91, 1940.
2. Jeans, P. C., and Cooke, J. C., Prepubescent Syphilis, New York, D. Appleton-Century Company, 1930, p. 168.
3. O'Leary, P. A., Gastric syphilis, Am. J. Surg. **11**:286, 1931.
4. Rafsky, H. A., Weingarten, M., and Herzig, W. F., Syphilis of stomach: Review of gastroscopic findings and intragastric photographs in color, Rev. gastroenterol. **15**:359, 1948.
5. Bockus, H. L., and Bank, J., Upper gastro-intestinal disease associated with syphilis, J.A.M.A. **90**:175, 1928.
6. Behrendt, H., Diagnostic tests for infants and children, New York, Interscience Publishers, Inc., 1949, p. 9.
7. Palmer, W. L., Schindler, R., Templeton, F. E., and Humphreys, E. M., Syphilis of stomach: Case report, Ann. Int. Med. **18**:393, 1943.

SPANISH ABSTRACT

Goma del Estómago en la Sífilis Congénita

Los autores relatan el caso de un niño de 11 años con historia de vómitos inmediatos o tardios, intermitentes, con 16 meses de evolución y dolor intenso, también intermitente, localizado al cuadrante superior izquierdo del abdomen: ambas manifestaciones desaparecían por periódos de 2 a 3 semanas. El enfermo había perdido alrededor de 14 kilos en los 2 últimos años. La madre tenía reacciones serológicas para la sífilis positivas. La exploración física, excepción de su desnutrición, fué negativa; sus reacciones de Kahn y Kolmer positivas. Endoscópicamente se visualizó una lesión granulosa enrojecida y friable de la gran curvatura del estómago, cuyo estudio histológico reveló tejido inflamatorio crónico. La radioscopía demostró deformación que recordaba un nicho en el tercio medio de la curvatura mayor del estómago con ausencia de ondas peristálticas a dicho nivel. En vista del fracaso de la prueba terapeútica por 14 días con 300.000 unidades de penicilina cada 12 horas y 5 gotas diarias de solución saturada de ioduro de potasio, se le hizo extirpación de dos tercios del estómago un mes mas tarde. Excepción de un episodio de Keratitis intersticial derecha que rápidamente cedió a la aplicación tópica de cortisona en el segundo día del postoperatorio evolucionó satisfactoriamente ganando 4 ½ kilos al salir del hospital, 3 semanas después de operado y 3 meses después estaba aparentemente sano. El estudio de la porción gástrica excindida reveló una ulceración anular de la mucosa cuyas características anatómicas e histológicas eran compatibles con el diagnóstico de goma del estómago.

Aunque rara, esta lesión ha sido ya reportada como una manifestación de sífilis congénita.

Una historia de vómitos, dolor abdominal crónico intermitente y pérdida de peso, en un niño con reacciones serológicas sifilíticas positivas sugiere la posibilidad de una sífilis gástrica y la demostración radiológica de una lesión constrictiva del estómago, aclorhidria gástrica, y el hallazgo gastroscópico de una lesión granulosa, roja, friable y ulcerada apoya dicha posibilidad.

Conclúyese que si el tratamiento antiluético fracasa debe hacerse resección amplia del estómago a la mayor brevedad posible.

University of Texas—Medical Branch

CONGENITAL FAMILIAL NONHEMOLYTIC JAUNDICE WITH KERNICTERUS

By JOHN F. CRIGLER, JR., M.D., AND VICTOR A. NAJJAR, M.D.
Baltimore

OVER the past four years the authors have encountered a group of infants with a previously undescribed congenital abnormality, genetically determined. Because of its similarity to recognized entities, this abnormality has been given the descriptive name, congenital familial nonhemolytic jaundice with kernicterus. This is a report of seven patients, five of whom were admitted to this hospital. One was hospitalized elsewhere in 1932,* and the other was diagnosed by history.

These seven patients may be divided into three related family groups: family M., family H. and family T. This relationship was noted only after the authors had seen patients from all three families, and observed that they came from the same locality. Genealogic investigation of these three family groups revealed that they were all descendents of a couple M., the known affected infants appearing in the sixth generation (see chart 1). Since complete genetic studies have not been made, the exact incidence of this disease in earlier generations is not known. However, 15 probably affected individuals are shown in the family pedigree. The marriage in the third generation productive of 12 probably affected individuals was consanguineous, although we do not know the exact relationship of husband and wife. In order to eliminate the possibility of a mild latent jaundice, serum bilirubin determinations were obtained and found normal on the parents and 15 siblings of the affected infants.

The following are abstracts of the case histories of the six hospitalized patients.

CASE HISTORIES

Case 1.: L.M., a white female, was admitted at 5 wk. of age with jaundice present since the second day of life but asymptomatic until 5 days before admission. At that time she became anorexic, slightly febrile, and was said to have had 5 or 6 convulsions per day, each lasting 5 to 10 min. Aside from the intense jaundice, her physical examination was remarkably negative. Liver and spleen were not felt and no definite neurologic abnormalities were described. She did not seem ill.

Soon after admission, the neurologic symptoms became more apparent. Her inactivity was accompanied by increasing spasticity and rigidity of the extrapyramidal type. She lay in an opisthotonoid position and at times had difficulty in swallowing, requiring gavage feedings. Later she developed uncontrolled athetoid movements, but no convulsions were observed during her hospitalization. A liver biopsy was obtained at 17 wk. of age. After 16 wk. of hospitalization she was sent home unimproved and died shortly thereafter.

Case 2.: J.R.H., a white male, was admitted when 16 days of age because of persistent and intense jaundice since the second day of life. This was at first asymptomatic, but several days prior to admission, he became irritable, febrile, anorexic and occasionally vomited. There was intermittent slight umbilical bleeding. The family history revealed that the last of 3 siblings died at home when 26 days of age with jaundice of undetermined origin.

From the Department of Pediatrics, the Johns Hopkins University and the Harriet Lane Home, the Johns Hopkins Hospital, Baltimore.

(Received for publication March 22, 1952.)

* The Children's Hospital, Washington, D.C.

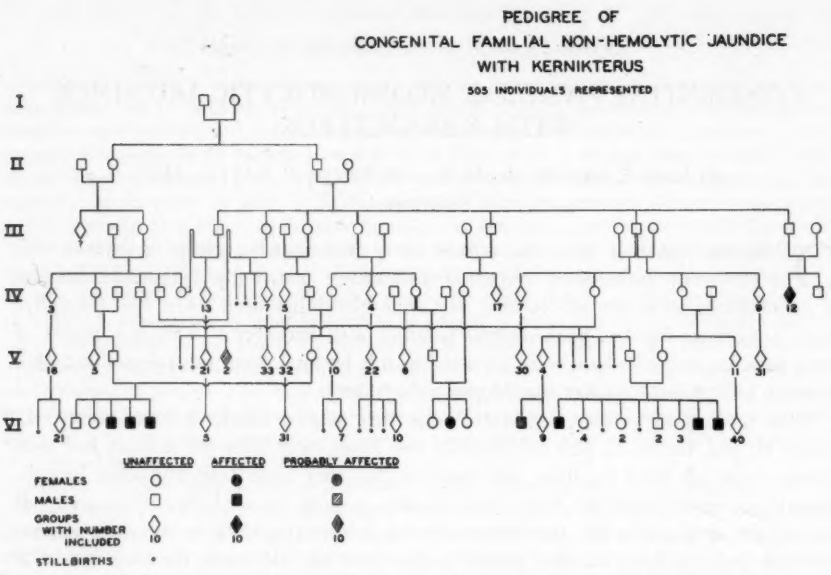


CHART 1. Pedigree of congenital familial nonhemolytic jaundice with kernicterus.

At the time of admission the patient was fairly well developed, but moderately ill, dehydrated and very much jaundiced. He had a temperature of 38.8° C., a slight mucoid nasal discharge and a few petechiae on the hard palate. There was a scab on the umbilical stump. The liver and spleen were not enlarged, and no abnormal neurologic findings were observed.

The patient lived for 36 hr., during which time he was maintained on parenteral fluids and treated with penicillin and streptomycin for a possible disseminated bacterial infection. Although his temperature dropped and he seemed slightly better, he remained rather listless. Twenty-four hours after admission he suddenly went into shock, vomiting coffee ground material. His temperature dropped to 34.5° C. He responded temporarily to oxygen, plasma, blood and heat therapy, but later died with a terminal elevation of pulse and a temperature of 40° C. Bacteriologic studies on the blood, urine and spinal fluid were negative. Autopsy showed no evidence of bacterial infection or cause for bloody vomitus. Pathologic changes in the brain and liver are described later.

The mother of this child subsequently gave birth to a fifth child who has the same defect and who is reported here as Case 3.

Case 3.: J.D.H., a white male, was admitted when 6 days old, because of jaundice of 3 days' duration and a family history of 2 similarly affected infants (see Case 2). Again the examination was remarkable only by the presence of marked icterus. The liver and spleen were not enlarged, and neurologic examination was within normal limits.

This infant remained in the hospital for 36 wk. The marked neurologic abnormality shown by the other infants was not evident in this child. During the early months of his life, it was believed that there might be minimal signs of extrapyramidal disease as shown by somewhat reduced and slowed spontaneous movement. However, no definite muscular rigidity or abnormal movements were noted. His development has since been within normal limits. A liver biopsy was obtained when he was 29 wk. old. He is now 18 mo. of age.

Case 4.: J.L.T., a white male, was admitted when 9 wk. old with persistent asymptomatic jaundice since the second day of life. He was seen in the Outpatient Department at 11 days of age when examination was essentially negative except for a marked degree of jaundice and somewhat hyperactive reflexes. Laboratory studies at that time revealed an icterus index of 100, Hgb. 14.2 gm./100

cc., bile present in the stools but absent in the urine. The serologic test for syphilis was negative. A tentative diagnosis of physiologic jaundice was made. Eventually he was admitted because of persistent jaundice. The family history revealed that the mother had 14 previous pregnancies, 2 of which terminated in miscarriages. The first child was similarly affected with jaundice and died when 11 mo. old in another hospital (Case 6). The 11 other siblings were living and well. The mother subsequently gave birth to her fourteenth living child (Case 5).

On admission, the patient was a well developed, well nourished infant who was very much jaundiced but did not appear ill. Examination was otherwise negative. The liver and spleen were not enlarged and neurologic examination was not remarkable.

The patient was hospitalized for 43 wk., and is the second one observed so far who lived beyond 1 yr. of age. During the first few weeks of observation, neurologic signs of kernicterus became increasingly evident. His face became expressionless and muscle tone increased. He lay almost constantly with his head drawn backwards and his back arched. Later he developed intermittent, uncontrolled perking movements of the arms and legs which required padding of the crib sides to prevent injury. The progression of these neurologic signs was slow. However, by 5 or 6 mo. of age they were quite marked. The course of his hospitalization was characterized by bouts of hyperpyrexia, sometimes associated with mild respiratory infection, but more often unexplained, subsiding either spontaneously or with the use of a sedative such as phenobarbital. A liver biopsy was obtained at 11½ mo. of age. Following this procedure, the patient was sent home and died 4 mo. later of a sudden, unexplained febrile illness.

Case 5.: L.T., a white male, was admitted when 17 days old because of persistent jaundice similar to that of 2 siblings (Cases 4 and 6). Again the jaundice appeared on the second day of life and was asymptomatic until the tenth day, when he developed an upper respiratory infection associated with occasional vomiting and loose stools. For this he was given penicillin and put on cow's milk formula. The symptoms subsided, but the jaundice persisted and became more marked.

Marked jaundice without hepatic or splenic enlargement was evident on examination. In this patient, however, central nervous system involvement was already quite apparent at the time of admission. The neurologic picture was well described in a note by Dr. Frank Ford* written when the patient was 2 mo. old. "His face is somewhat immobile. There seems to be some reduction of spontaneous activity. At times distorted postures are seen which may persist for some minutes. These are similar to those seen in athetosis. Occasionally one sees very slow writhing movements of smaller amplitude of the trunk and extremities. These include retraction of the head and extension of the trunk, extension of the arms, flexion of the wrists, over-pronation and hyperextension of the fingers. On passive movement one encounters a variable degree of muscular rigidity. No facial grimaces are seen in contrast to athetosis in which facial grimaces are prominent. The tendon reflexes are not specially altered. The grasp reflexes are not well developed. No tonic neck reflexes are elicited."

This patient remained in the hospital until he died at the age of 29 wk. As in his brother's case (Case 4), the course was complicated by frequent febrile episodes, which seemed to respond more readily to sedation than to any one antibiotic or a combination of antibiotics. With these febrile seizures, he would become increasingly irritable and eat poorly, although at no time did he seem to have a specific swallowing defect. Repeated attempts, bacteriologically and otherwise, to establish a cause for these spells of fever were unsuccessful. He died in an unexplained episode, his temperature rising to 43° C. terminally. Permission for autopsy was not given. A biopsy of the liver, however, was obtained when he was 15 wk. old.

Case 6.: J.J.T., a white male, and first of 14 siblings, including Cases 4 and 5, was hospitalized elsewhere in 1932 at the age of 39 wk. He had a history of jaundice present from birth, associated with diffuse central nervous system damage appearing shortly after birth and becoming progressively more marked. He was admitted because of a 4 day febrile illness, associated with 2 convulsive episodes.

Examination was reported as showing a restless, irritable, acutely ill infant with marked jaundice. The pharynx was injected, and there was bilateral otitis media. The liver and spleen were not felt.

---

* Appreciation is due to Drs. Frank Ford and David Clark of the Department of Neurology for their valuable opinions regarding the neurologic picture shown by these infants.

TABLE 1

RESULTS OF HEMATOLOGIC TESTS

		Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age on admission (wk.)		5	2.5	1	9	3	39
Serum bilirubin—mg./100 cc. (van den Bergh)	total	37.2	25.8	27.4*	34.0	44.8*	ict. index 50
	indirect	33	23.8	27.4	32.0	44.8	+
Blood group studies†	mother	O Rh. pos	A_1N Rh_1	A_1N Rh_1	AB Rh pos.	AB Rh pos.	AB Rh pos.
	patient	A_1MN Rh_0	A_1N Rh_2	A_1N Rh_2	AN Rh_1Rh_2	ABN Rh_1Rh_2	—
	Coomb's test	—	neg.	neg.	neg.	neg.	—
Hemoglobin—gm./100 cc.		14.5	14.5	16.5	12.5	15	9
Hematocrit—%		—	—	52	31	51	—
Blood smears	peripheral	normal	normal	normal	normal	normal	normal
	bone marrow	—	normal at autopsy	normal	normal	normal	—
Reticulocytes—%		1.0	—	0	0.8	0.1	—
RBC Fragility— saline		normal 0.48–0.39	—	normal 0.48–0.30	normal 0.48–0.30	—	normal 0.42–0.28
Stool	bile	present	present	present	present	present	present
	urobilin excretion	normal values	—	normal values	normal values	normal values	—
Urine	bile	absent	absent	absent	absent	absent	absent
	urobilinogen	normal	—	normal	normal	normal	normal

* Measured spectrophotometrically.[3]

† Through the courtesy of the Baltimore Rh Type Laboratory.

— Not done

TABLE 2

RESULTS OF HEPATIC FUNCTION TESTS

Patient	Age (wk.)	Serum Bilirubin mg./100 cc. Indirect	Bilirubin Excretion % Retention After 4 Hr.	Bromsulfalein Excretion mg./100 cc. Retention 30 min.	Cephalin Flocculation	Thymol Turbidity Units	Prothrombin Time % Normal	Galactose Tolerance	Alk Phosphatase Bodansky Units	Pathology	
										Bile Thrombi in Canaliculi	Slight Periportal Fibrosis
Normal	>12	0.8–1.2	<10	<10% or <1.0 mg./100 cc.	neg.	<6	50–100	<40 mg./100 cc.	5–15	absent	absent
1. L.M.	6	37.2	—	—	+	2.1	60	—	11.3	—	—
	18	27.6	—	7%	neg.	4.2	100	—	10	present	present
2. J.R.H.	2.5	25.8	—	—	neg.	2.7	50	—	—	present	absent
3. J.D.H.	1	27.4	—	—	neg.	0.5	100	—	19.4	—	—
	9	17.5	—	3.4	—	—	—	—	—	—	—
	14	17.5	40	—	—	—	—	normal	—	—	—
	24	17.2	—	0.3	neg.	0.8	—	—	20.6	—	—
	35	20.6	17	—	—	—	—	—	—	present (29 wk.)	absent
4. J.L.T.	9	33	—	4.9	neg.	0.4	100	—	12.6	—	—
	13	19	—	1.2	neg.	0.7	—	—	14.6	—	—
	38	21	—	0.3	neg.	1.3	100	—	14.2	—	—
	42	31	—	0.5	neg.	0.5	78	—	18.4	—	—
	50	33	—	—	—	—	—	—	—	present	absent
5. L.T.	3	44.8	—	—	neg.	0.6	—	—	30.0	—	—
	12	16	—	0.9	—	—	—	—	—	—	—
	14	15.7	24	—	—	—	—	—	—	present	present
	18	12.6	—	0.1	neg.	1.4	—	normal	16.4	—	—
6. J.J.T. 1932	46	ict. index 50 van den Bergh "indirect"	—	—	—	—	—	—	—	present	present

—Not done.

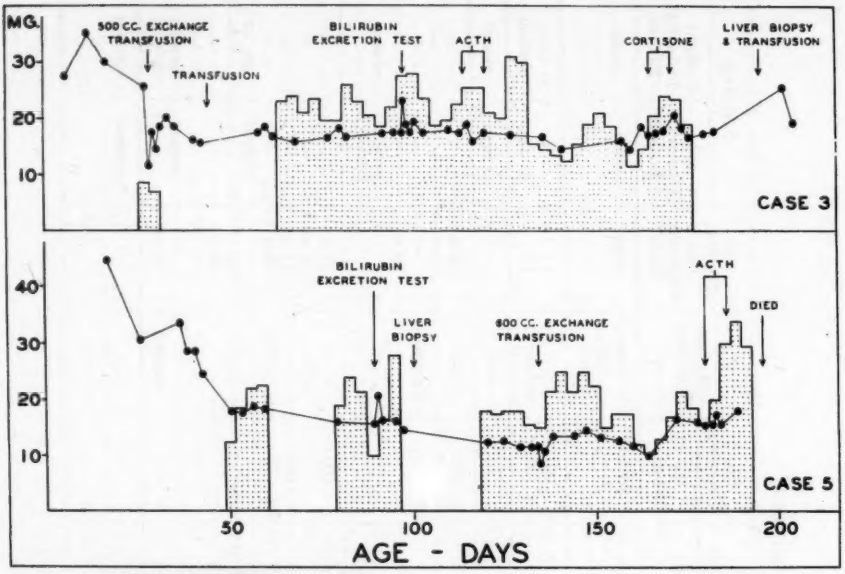


CHART 2. Serum bilirubin levels and urobilin excretion in 2 patients (Cases 3 and 5).

The head was markedly retracted and the extremities were held in flexion. There was considerable muscular rigidity at times. The baby's development was retarded.

The patient lived for 8 wk. after admission. His respiratory infection subsided initially, but later there was a terminal exacerbation. An autopsy was obtained and this showed the presence of a diffuse atelectatic pneumonia. The brain was not examined and changes in the liver are discussed elsewhere.

LABORATORY DATA

Laboratory studies on the 6 patients are summarized in tables 1 and 2 and charts 2 and 3. These infants were studied during the newborn period and at intervals up to 1 yr. of age. During this time of life there is normally a wide physiologic variation in the standard values for hematologic and liver function tests. Consequently, the initial laboratory findings and the age of the patients on admission are included in table 1. These results are characteristic of the patients at the different ages. More complete data on serum bilirubin and liver function studies are given in table 2 and charts 2 and 3.

Blood group studies* shown in table 1 were made on Cases 1 to 5, and with one exception, showed no incompatabilities. In Case 1, an anti-A titre of 1:4,000 was demonstrated, but it was believed that this process played no essential part in the jaundice which persisted throughout life and was not associated with evidence of increased hemolysis. Studies for evidence of increased hemolysis (see table 1), including red cell fragilities, reticulocyte counts, bone marrow examinations, and semiquantitative determinations of stool and urine for urobilin and urobilinogen gave normal results.

Serum bilirubin levels in the six patients ranged between 10 and 44 mg./100 cc. (see table 2 and chart 2). Although there was an increase of 2 to 4 mg./100 cc. in the direct bilirubin (measured by the van den Bergh reaction, table 1), the greater portion of the serum bilirubin was of the

* Through the courtesy of the Baltimore Rh Typing Laboratory.

indirect type. The slight increase in the direct bilirubin associated with an equally slight elevation of the alkaline phosphatase activity in Cases 3, 4, and 5, is possibly explained by the pathologic finding of bile thrombi in canaliculi and more rarely in larger ducts (see Pathology). These pathologic changes, however, offer no satisfactory explanation for the much more striking finding of high indirect serum bilirubin. The height of serum bilirubin levels and the urobilin excretion in 2 of the patients in relation to various studies are shown in chart 2.* High bilirubin levels obtained

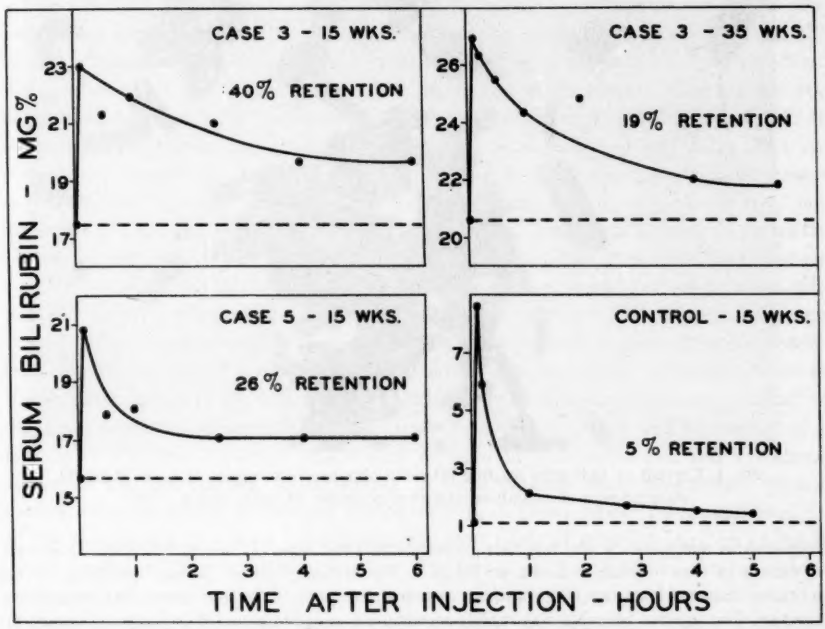


CHART 3. Bilirubin excretion tests in 2 patients compared with that of normal infant of about same age. Commercial bilirubin 5 mg./kg. body weight dissolved in 0.1 M. sterile sodium carbonate and injected intravenously.

in the neonatal period are undoubtedly related to the superimposition of factors responsible for physiologic jaundice in newborn infants. Once this period is over (between 4th and 12th week of life), these levels become remarkably fixed, with some tendency, nevertheless, to rise later in the first year or before death. This rise was most marked in Case 4 between 38 and 42 weeks, and was unexplained and not correlated with other liver function tests (table 2). In 2 of the patients (Cases 3 and 5), bilirubin excretion tests[2] were done. The bilirubin was measured spectrophotometrically.[3] The results of these tests compared with those of a normal infant of 15 wk. are shown graphically in chart 3. The tests show quite definitely an abnormal retention of injected bilirubin. Other liver function studies reported in table 2 are within normal limits for age.

Irregular determinations of the serum NPN, calcium, phosphorus, sodium, potassium, carbon dioxide combining power, chloride and cholesterol, not shown in these tables, were normal.

Besides these more usual tests, an effort was made to study the chemical nature of the bile pigments. This was done by isolating, in crystalline form, the pigment from the serum of some of these patients. The crystalline indirect bilirubin so isolated had the same physical and chemical

* The authors are indebted to Dr. Hugh Josephs for the stool urobilin determinations. The method used was a fluorophotometric modification of his earlier procedure.[1]

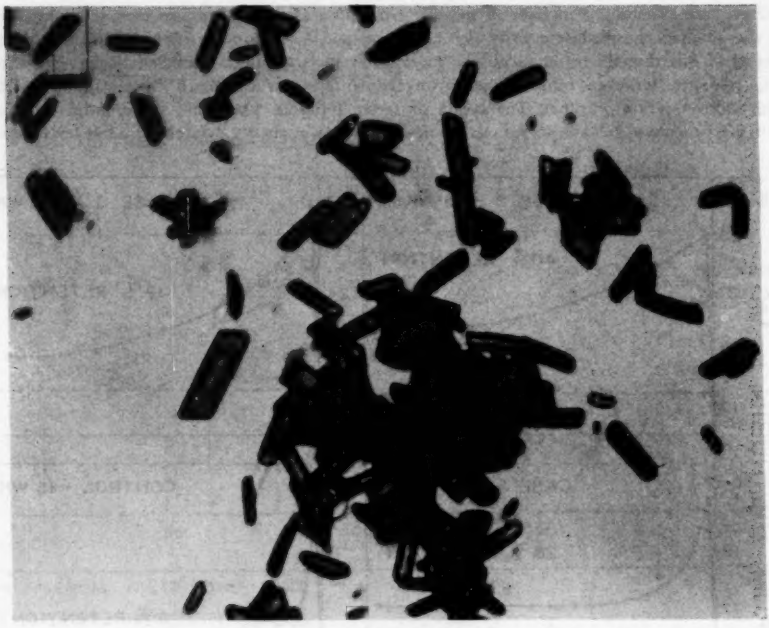


FIG. 1. Crystals of indirectly reacting bilirubin obtained from serum of L. T. (Case 5), showing type of crystals encountered normally. Magnification x 1700.

properties as that similarly obtained from patients with other types of indirect bilirubin—jaundice.[3, 4] A picture of these crystals is shown in Figure 1. Furthermore, 100 cc. plasma containing 11 mg. bilirubin, removed from one of the patients, was injected into a 2 mo. old infant with normal liver function. The injected bilirubin was rapidly metabolized, suggesting that it is a pigment which can be handled by a normally functioning liver.

PATHOLOGY*

Five of the 6 patients died, but autopsies were obtained in only 2 (Cases 2 and 6). Both of these died before the entity was recognized, and pathologic material for review was available only in Case 2. In the other one, however, a complete report was made at the time of death, although the pathologic material was discarded. In the remaining patients, liver biopsies were obtained by operative exploration.

Microscopic examination of liver tissue from these infants did not show obvious histologic changes. The most striking and only universal finding was the presence of bile thrombi in the hepatic canaliculi. The degree of this abnormality varied and did not seem particularly related to the age or degree of jaundice. In Patient 3, bile thrombi were also described in the hepatic ducts. In Cases 1, 5 and 6, slight periportal fibrosis was observed in some areas, but was by no means diffuse.

The brain was examined in only one patient (Case 2). It was described as showing deep jaundice of the cerebral cortex, thalamus, corpus striatum, mammillary bodies, dentate nucleus and inferior olive. Microscopically, the basal ganglia showed fat droplets in the nerve cells, but the changes were not remarkable.

* The authors are indebted to Drs. A. R. Rich and S. Eversole for the careful and thorough review and study of the pathologic material in these cases. Their helpful suggestions and comments are greatly appreciated.

In neither of the two autopsied patients was there evidence of any hemolytic disease. In Patient 2, who died at 17 days of age, however, there was a moderate splenic hemosiderosis and also hemosiderin in the Kupffer cells of the liver. This was thought to be normal and due to physiologic blood destruction at this age. The bone marrow was not hyperplastic and no iron was present in the kidney section.

Discussion

The most common causes of jaundice in infancy can be eliminated because of its prolonged and intractable character, the absence of blood group incompatabilities, and the lack of pathologic evidence of either hemolytic disease or primary biliary obstruction. There is no reason to consider an infectious origin and in the absence of pathologic evidence, congenital cirrhosis can be excluded. We are, therefore, left with what appears to be primarily a physiologic rather than histologic abnormality of the liver. This abnormality is genetically determined and is revealed by a persistently elevated indirect serum bilirubin and by an abnormal bilirubin excretion test. In all the patients, bile thrombi were seen in few bile canaliculi, and in three, a minimal amount of periportal fibrosis of the liver was also present. It is felt, however, that these histologic changes are merely associated pathologic findings and are not the primary cause of jaundice, particularly when the pigment is predominantly of the indirect type. The presence of severe central nervous system damage in all but one of these patients suggests that this association may be evidence of a diffuse metabolic defect. It is impossible at present, however, to determine whether the neurologic abnormality is a coexisting anomaly, a result of the same fundamental metabolic disorder or is secondary to hyperbilirubinemia. It is regrettable that this important relationship between hyperbilirubinemia and kernicterus cannot be clarified further. Its occurrence in these patients does, nevertheless, present further evidence against its being a specific finding in blood group incompatabilities.[5]

The prognosis is very poor. Febrile episodes, most likely of central origin, are common. These seemed to respond best to sedation. Patients 2, 4, 5 and 6 died during such an acute spell of fever and only in Case 6 was there any definite evidence of infection. It seems likely, therefore, that the extent of the central nervous system disease is probably an important factor in determining the duration of the patient's life. To date, with two exceptions (Case 3 and 4), the patients died within the first year of life. One of these died at 15 months of age (Case 4). The other (Case 3), at the time of this writing, is 18 months old.

Several therapeutic measures were tried, in the hope that if successful, they might alter the abnormality to the benefit of the patient and perhaps shed some light on the cause of the disease. Exchange transfusions were performed in Cases 3 and 5 (see chart 3) producing only temporary (less than 24 hours) lowering of the serum bilirubin. Although of no value therapeutically, these procedures suggest that there is a threshold of bilirubin excretion in these patients. Adequate trials of ACTH in Cases 3 and 5 and of cortisone in Case 3 produced no significant change in the patient or the jaundice. Intensive liver extract therapy in Case 3 had no effect.

This entity most closely resembles that previously described by a number of investigators under a variety of names including Gilbert's disease, physiologic hyperbilirubinemia, icterus intermittens juvenalis, constitutional hepatic dysfunction and familial nonhemolytic jaundice.[6-9] All of these refer to patients seen usually in late childhood or early adult life, complaining of fatigue and asthenia and having a chronic, usually

TABLE 3

COMPARISON OF FINDINGS IN FAMILIAL NONHEMOLYTIC JAUNDICE WITH THOSE IN CONGENITAL FAMILIAL NONHEMOLYTIC JAUNDICE WITH KERNICTERUS

	Congenital Familial Nonhemolytic Jaundice with Kernicterus	Familial Nonhemolytic Jaundice
1. Genealogy	Recessive (described in only 1 family)	Probably dominant
2. Onset	At birth	Probably at birth but usually discovered in young adults
3. Associated CNS involvement	Always (1 possible exception)	None
4. Prognosis	Very Poor	Good
5. Jaundice	Marked	Usually mild
6. Serum bilirubin	10–44 mg./100 cc.	2–15 mg./100 cc. Usually under 5 mg./100 cc.
7. Bilirubin function test	Delayed excretion	Delayed excretion
8. Other liver function tests	Normal	Normal
9. Evidence of increased hemolysis	None	None
10. Histologic evidence of liver pathology	Bile thrombi in canaliculi 6 cases Slight periportal scarring 3 cases	None

mild, nonhemolytic, acholuric retention jaundice. A comparison is shown in table 3. The differences in mode of inheritance, age of onset, presence of central nervous system damage, prognosis, and degree of jaundice with the presence of pathologic changes serve to distinguish between these two familial abnormalities, although the similarity in the type of jaundice is obvious. There has been speculation as to the cause of familial nonhemolytic jaundice. In these cases, a genetic mutation is indicated although the underlying defect is still obscure. It appears that the liver in such cases is unable to excrete bilirubin at a normal rate. This results in an accumulation of the pigment in the serum until it reaches a threshold level above which its excretion, as measured by urobilin, approaches normal amounts.

SUMMARY

Seven patients with congenital familial nonhemolytic jaundice with kernicterus are presented. Six of these were hospitalized and studied. One was diagnosed by history. The abnormality appears to be genetically determined, being inherited most likely as a lethal recessive characteristic. The only abnormal laboratory findings are pronounced elevation of indirect serum bilirubin and delayed excretion of injected bilirubin. Pathologically, bile thrombi in the canaliculi were found in all patients studied, with very slight periportal fibrosis present in the liver sections from Cases 1, 5 and 6. In the single

brain examined, Case 2, kernicterus was described. The prognosis is extremely poor, the patients generally dying in the first year of life. No therapeutic measures have been found helpful. The similarity to a previously described disease, familial nonhemolytic jaundice, is discussed.

References

1. Josephs, H. W., Urobilin excretion of infancy and childhood: Relation to blood destruction and formation, Bull. Johns Hopkins Hosp. **55**:154, 1934.
2. Weech, A. A., Vann, D., and Grillo, R. A., Clearance of bilirubin from plasma: Measure of excreting power of liver, J. Clin. Investigation **20**:313, 1941.
3. Najjar, V. A., Metabolism of bilirubin and related compounds, PEDIATRICS, to be published.
4. Najjar, V. A., Crystallization and properties of "direct" and "indirect" bilirubin from human serum, Fed. Proc. **10**:227, 1951.
5. Zuelzer, W. W., and Mudgett, Roxie T., Kernicterus: Etiologic study based on analysis of 55 cases, PEDIATRICS **6**:452, 1950.
6. Dameshek, W., and Singer, K., Familial non-hemolytic jaundice: Constitutional hepatic dysfunction with indirect Van Den Bergh reaction, Arch. Int. Med. **67**:259, 1941.
7. Menlengracht, E., Review of chronic intermittent juvenile jaundice, Quart. J. Med. (New Series) **16**:83, 1947.
8. Rozendall, H. M., Comfort, N. W., and Snell, A. M., Slight and latent jaundice, J.A.M.A. **104**: 374, 1935.
9. Carithers, H. A., Jr., Non-hemolytic familial jaundice: Report of family, J. Pediat. **19**:817, 1941.

Spanish Abstract

Ictericia Congénita Familiar no Hemolítica con Kernicterus

Los autores del artículo dan este título a un cuadro clínico y de laboratorio que encontraron en siete enfermos durante los últimos cuatro años. Los casos provenían de tres familias emparentadas entre si, pues en su arbol geneológico se comprobó que eran descendientes de un matrimonio y los primeros niños enfermos conocidos aparecieron en la sexta generación. Aunque no se investigó su incidencia exacta en generaciones más tempranas, es probable que hayan sido afectados 15 individuos. En la tercera generación hubo un casamiento consanguíneo, sin saberse el parentezco exacto entre los cónyuges, que dió nacimiento a 12 personas probablemente afectadas. En la posibilidad de que se tratara de un estado de ictericia moderada latente se hicieron determinaciones de bilirrubina en el suero sanguíneo de los padres y 15 parientes de los niños enfermos pero se encontraron valores normales.

El cuadro clínico era característicamente similar en todos los casos: ictericia desde el segundo día de la vida, asintomática, sin alterar el estado general, sin hepato ó esplenomegalia, ni síntomas de anemia. En 4 de los casos existía Kernicterus con manifestaciones varias en diferentes grados: espasticidad, rigidez, opistótonus cara inexpresiva, movimientos bruscos incontrolables, motilidad disminuida, extensión de los brazos, con flexión de muñecas, pronación exagerada de manos e hiperextensión de los dedos. La evolución del cuadro era modificado por episodios de hipertermia, comunmente sin explicación infecciosa aparente. Un solo caso vivía aún a los 18 meses de edad y sin Kermicterus, la muerte mas temprana se registró a los 18 días de edad.

Los niveles de bilirrubina en sangre oscilaron entre 10 y 44 mlgs.%, casi toda la bilirrubina era indirecta, pues la directa nunca fué major de 2—4 mlgs.%. Los niveles mas altos correspondieron al periodo neonatal al final del primer año o pre-morten, siendo bastante uniforme en el resto del tiempo. Excepción hecha de la prueba de excreción de bilirrubina que demostró una retención definitiva de la bilirrubina inyectada las demás pruebas de funcionamiento hepático estaban dentro de límites normales. Las propiedades fisico-químicas de los cristales de bilirrubina obtenidos de varios de estos enfermos eran iguales a las de otros enfermos con bilirrubina indirecta de otro origen y cuando se inyectó plasma con 10 mlgs. de bilirrubina de uno de los casos en un niño sano de 2 meses de edad, ésta fué metabolizada rápidamente lo cual sugiere que el hígado normal es capaz de hacerlo. Las determinaciones de grupos sanguíneos y Rh demostraron ausencia de incompatibilidad

y no pudo comprobarse por los estudios de fragilidad de los eritrocitos, reacción reticulocitaria, mielograma y de la urobilina y urobilinógeno fecal y urinario la intervención de un factor hemolítico.

Las lesiones histopatológicas hepáticas no explicaron el proceso patológico, pues consistieron fundamentalmente en trombos biliares en los canalículos sin relación con el grado o edad de la ictericia, y ligera fibrosis periportal en algunos de los casos. La impregnación biliar en los centros de la base del cerebro y en la corteza cerebral fue evidente en la única autopsia realizada en un caso con Kernicterus.

En conclusión, es facil eliminar las causas mas comunes de ictericia en la infancia por su característica de persistencia y prolongación, ausencia de incompatibilidad de grupo sanguíneo y falta de pruebas a favor de un proceso hemolítico ó de obstrucción biliar primitiva; igualmente, no puede sostenerse su origen infeccioso o la posibilidad de la cirrosis hepática congénita. En consecuencia, por exclusión puede aceptarse que se trate de una anormalidad fisiológica primitiva, mas bien que de una anormalidad histológica hepática, la cual sería heredada como un caracter recesivo letal y que se acompaña casi siempre de Kernicterus, sin poder asegurar si es primitivo o secundario a la hiperbilirrubinemia. Además, es un padecimiento de pronóstico grave y con episodios febriles frecuentes muy probablemente de origen nervioso central, que responden mejor a los sedantes y ya que 4 de los casos murieron en uno de estos episodios y solamente en uno había una infección evidente, es muy posible que la extensión de las lesiones del sistema nervioso central sea un factor importante en relación con la prolongación de la vida. Las exsanguino-transfusiones solo produjeron reducción temporal de la bilirrubinemia lo cual hace sugerir que estos enfermos tienen un umbral de excreción para la bilirrubina. El hígado es incapaz de excretar este pigmento al ritmo normal lo cual determina su acumulación en el suero hasta que alcanza un nivel por encima de dicho umbral realizándose entonces su eliminación con un ritmo normal como puede medirse por la urobilina. Ninguna respuesta se obtuvo con la cortisona, A.C.T.H. o extracto hepático.

El padecimiento se semeja mucho al cuadro descrito como enfermedad de Gilbert, hiperbilirrubinemia fisiológica, ictericia intermitente juvenil, disfunción hepática constitucional e ictericia no hemolítica familiar, que generalmente se ye en la adolescencia o en el adulto joven que se queja de fatiga y astenia y presenta ictericia crónica acolúrica por retención, no hemolítica, generalmente moderada, familiar, heredada como caracter probablemente dominante, de buen pronóstico y no asociado con lesión del sistema nervioso central, lo que permite hacer sin dificultad su diferenciación.

The Johns Hopkins Hospital

REACTIVITY OF THE SKIN OF THE NEWBORN INFANT

By ABE MATHESON, M.D., MARVIN NIERENBERG, M.D.,
AND JOSEPH GREENGARD, M.D.
Chicago

REPORTS by investigators on the reactivity of the skin of newborn infants are contradictory and frequently confusing in their interpretation. Is the skin of these newborn infants capable of reacting to dermal irritants or specific antigens? Is it capable of demonstrating whealing reactions as does the skin of older children or adults? These and similar questions prompted the authors to attempt clarification of the subject. Various nonspecific antigens and dermal irritants were tested by Adelsberger[1] and by Friedberger and Heim.[2] These investigators found that the neonatal skin was sluggish in its reaction to those materials which uniformly produced clearcut reactions in the adult. When primary toxic substances derived from Cl. diphtheriae, scarlet fever streptococci, staphylococci and gonococci were used intradermally, the skin reaction obtained was usually found to be reduced or negative. According to Ruh and McClelland,[3] Cooke,[4] Kobak and Pilot[5] and Kobak and Greengard,[6] this failure of response was considered not to be due to protective antibodies.

In the case of atopic antigens similar findings have been recorded. Balyeat[7] in 1928 tested 119 newborn infants under 3 days of age with milk, wheat and egg antigen, and reported one positive reaction to milk and one to egg. Similarly, Walzer and his associates[8] in a study of 100 infants under 10 days of age by scratch and intradermal technic with milk, wheat and egg, concluded that the erythema responses found in some were not specific. They found no significant positive reactions. In a series of 150 cases Zohn[9] likewise demonstrated the failure of infants to respond with wheals to intradermal testing employing wheat, milk and egg. Twenty-five of these infants were tested intradermally to wool, feathers and dust without whealing, though some erythema reactions were noted. Smyth and Bain[10] tested 125 newborn infants with milk, egg and wheat and found negative reactions in all. On the other hand, Carey and Gay[11] stated that the skin of the newborn child is capable of whealing but to a lesser extent than that of older children or adults. Using passive transfer technic, they demonstrated the ability of the newborn infant to develop localized skin sensitivity to ragweed. These reactions did not differ appreciably from those of the adult, whealing being produced with higher concentrations of reagin and antigen. Sulzberger and Baer[12] tested eight newborn infants intradermally with 1:1000 histamine solution and were convinced that their skin was capable of whealing. However, there were no parallel control tests using older children and adults and the solutions used were concentrated.

The present investigators' general plan of investigation consisted of the following procedures:

1. Skin tests on newborn infants with serial dilutions of histamine and comparison of the results with similar testing of older children.

From the Sarah Morris Hospital for Children of the Michael Reese Hospital, Chicago.
Supported in part by the Jesse Werthamer Fund for Allergy.
(Received for publication Oct. 19, 1951.)

TABLE 1

REACTIVITY OF SKIN OF NEWBORN INFANT TO GRADED DILUTIONS OF HISTAMINE APPLIED BY SCRATCH TEST

Histamine Dilutions	1 8000	1:16000	1:32000	1:64000	1:128000	1:256000	1:512000	Control	
Case No.	E* cm.	E	E	E	E	E	E	E	W†
1.	1.5	1.5	1.0	2.0	2.0	1.5	1.5	0	
2.	3.0	2.5	2.5	1.5	1.5	1.0	0	0	
3.	3.0	3.0	4.0	2.0	2.0	2.0	2.5	0	
4.	2.5	3.5	3.0	2.5	3.0	2.0	1.5	1.0	
5.	1.5	2.0	2.0	1.5	1.5	1.0	0.5	0	
6.	2.5	1.0	1.0	2.0	1.0	0.75	0.5	0	
7.	2.5	2.0	2.0	2.0	1.5	2.0	1.5	0	
8.	3.0	2.5	2.5	1.5	1.5	1.5	1.5	1.0	
9.	3.0	3.0	2.0	1.5	2.0	1.5	1.5	0.5	
10.	1.5	1.5	1.5	1.0	1.0	1.0	1.0	0	
11.	3.0	3.0	2.5	3.5	3.0	1.5	0	0	
12.	2.0	1.5	2.0	1.5	2.0	1.0	1.0	0	
13.	1.5	1.5	1.5	0.5	0.5	0.5	1.0	0	
14.	4.0	3.5	3.0	1.5	1.5	1.5	1.5	1.0	
15.	3.0	2.5	1.5	1.5	2.0	1.5	1.0	0.5	
16.	1.5	1.5	0	2.0	0.5	0	0	0	
17.	3.0	2.5	2.0	2.5	2.0	2.0	1.5	0	
18.	2.5	2.5	2.5	1.5	1.0	1.0	1.0	0	
19.	4.0	0.5	0.5	0.5	0.5	0.5	0.5	0	
20.	2.5	1.5	1.0	1.0	1.0	1.5	1.0	0	
21.	0	0	0	0	0	0	0	0	
Positive	20	19	18	19	19	18	16	5	0
Per Cent Positive	95	90	85	90	90	85	76	23	0
Ave. Size Positives	2.6	2.2	2.1	1.7	1.8	1.4	1.28	0.8	

* E—Erythema.

† W—There was no whealing present in any of these cases.

2. Fixation of reagin by skin of newborn infants—full term and prematurely born.

3. Demonstration of cutaneous reactions in passively sensitized sites of newborn infants, following the ingestion of the specific antigen. Comparison of the results with same technic in older children.

4. Demonstration of cutaneous reactions in passively sensitized sites of newborn infants, following the subcutaneous injection of the specific antigen.

INVESTIGATIONS

1. Reactivity of the Skin of the Newborn Infant to Serial Dilutions of Histamine as Compared to That of Older Children.

PROCEDURE

Normal newborn infants, both Negro and white, of both sexes, varying in age from several hours to 5 or 6 days, were selected at random. Scratch tests with dilutions of histamine were made

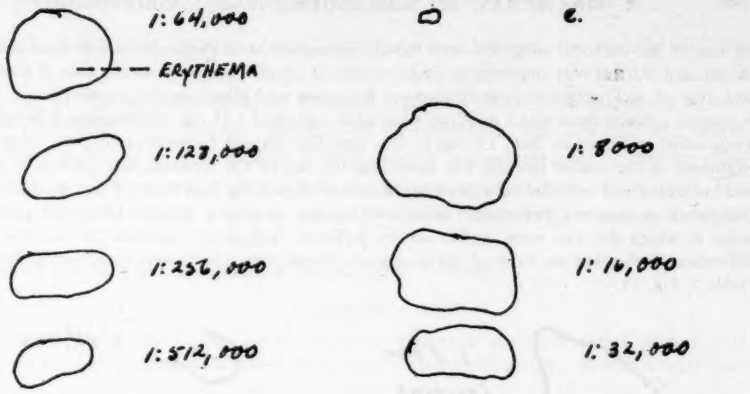


FIG. 1. Typical tracing of reactions to dilutions of histamine applied to skin of newborn infant by scratch technic.

TABLE 2

SKIN REACTIVITY OF 27 CHILDREN OF PRESCHOOL AGE TO GRADED DILUTIONS OF HISTAMINE APPLIED BY SCRATCH TEST

Histamine Dilutions	1:8000		1:16000		1:32000		1:64000		1:128000		1:256000		1:512000		Control	
Case	E cm.	W cm.	E	W	E	W	E	W	E	W	E	W	E	W	E	W
1.	3.5	1.0	2.5	0	1.5	0	2.0	0	1.5	0	2.0	0	0.5	0	0	0
2.	2.5	0	2.0	0	2.0	0	2.0	0	1.0	0	1.0	0	0.5	0	0	0
3.	3.0	0	2.5	0	2.0	0	1.5	0	2.0	0	1.0	0	1.0	0	0	0
4.	2.5	1.0	2.0	0	1.0	0	1.5		1.5		2.0		1.5		1.0	
5.	3.5	1.0	2.0	0	2.5	0	1.5		1.0		0		0.5		0	
6.	2.0	1.5	2.0	0	2.0	0	1.5		1.0		1.0		1.0		0	
7.	3.0	2.0	0	0	1.5	0	1.5		0.5		0		0		0	
8.	2.5	0	1.5	0	0.5	0	0		0		0		0		0	
9.	3.0	0.5	2.0	0	1.5	0	1.5		1.5		1.0		1.0		0	
10.	2.5	0	2.0	0	1.5	0	2.0		1.5		1.0		1.0		0	
11.	2.5	0	2.0	0	1.5	0	2.0		2.0		1.5		1.5		0.5	
12.	3.0	1.0	1.5	0	2.5	0	1.5		1.0		1.5		0.5		0	
13.	3.0	0	1.5	0	1.5	0	1.5		1.0		0.5		0.5		0	
14.	4.5	1.0	3.5	0.5	4.0	1.0	2.0		2.5		3.0		2.0		1.5	
15.	3.0	0	2.0	0	2.0	0	1.5		1.0		0.5		0.5		0	
16.	2.5	1.0	2.0	0	2.5	0	1.0		1.5		1.5		0.5		0.5	
17.	3.5	0	2.5	0	2.5	0	1.0		0.5		0.5		0.5		0	
18.	3.0	1.0	2.0	0	2.0	0	2.0		2.0		1.5		1.0		0.5	
19.	3.5	0	2.5	0	1.5	0	1.5		2.5		1.0		1.5		0	
20.	2.5	0	3.0	0	2.0	0	2.0		2.0		1.5		1.0		0.5	
21.	4.5	3.5	3.5	1.5	3.5	0	3.0		2.5		3.5		1.5		1.0	
22.	3.0	0	2.5	0	2.0	0	1.5		2.0		1.5		0.5		0	
23.	2.5	0	2.5	0	2.5	0	2.0		3.0		1.5		1.5		1.0	
24.	2.5	0	2.0	0	1.5	0	2.0		1.0		0.5		0		0	
25.	2.0	1.0	2.0	0	2.0	0	1.5		1.5		1.5		1.0		0	
26.	3.5	1.0	3.0	0	2.0	0	1.0		0.5		0.5		0		0	
27.	2.5	0.5	2.0	0.5	2.0	0.5	2.5		1.5		1.0		0.5		0	
Positive	27	14	26	3	27	2	26	0	26	0	24	0	23	0	8	0
Per Cent Positive	100	51.8	96.3	11	100	7.4	96	0	96.3	0	88.8	0	85	0	29.6	0
Ave. Size Positives	2.6	1.2	2.2	.8	1.9	.7	1.7		1.5		1.3		.9		.8	

E —Erythema.
W—Wheal.

by one of the authors, using the same technic throughout with particular care to minimize trauma. A standard scarifier was employed to make superficial circular abrasions on the skin of the back and one drop of each of the various dilutions of histamine was placed on the scarified areas. The basic histamine solution from which dilutions were made contained 2.75 mg. of histamine diphosphate*/cc. (equivalent to histamine base 1.0 mg.). The time that elapsed between placing the drops and the beginning of the visible reaction was noted and the size of the resultant skin reaction at its height was measured and recorded as a drawing. Reactions measuring less than 0.5 cm. in diameter were designated as negative. Physiologic saline solution was used as a control. In several instances the order in which the tests were applied on the back was reversed to eliminate the possible factor of differences in the skin reactivity of different areas. Twenty-one infants were examined in this manner (table 1, Fig. 1).

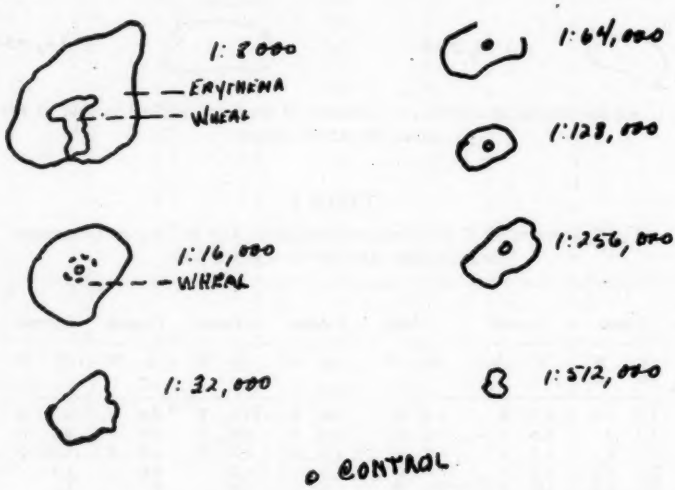


FIG. 2. Typical tracings of reactions to dilutions of histamine applied to skin of older child by scratch test.

In order to compare the reactivity of newborn infants to that of older infants and children, 27 patients of preschool age were chosen at random from a group hospitalized for other than medical reasons (i.e., elective surgery, orthopedic procedures, and convalescent surgical patients). These were both male and female, Negro and white. The same technic was employed as in the newborn infants (table 2, Fig. 2).

RESULTS

The findings in the 21 newborn infants tested are presented in table 1. With one exception (Patient 21, who failed to react) all revealed positive tests with erythema greater than 1 cm. in diameter in dilutions up to 1:256,000. In the 1:512,000 dilution there were four negative reactors. Five of the control tests were positive. Whealing did not occur in any case. The reactions were in the form of an erythematous flare reaching its height in 10 minutes and disappearing in one-half hour. Six of the infants whose mothers had a history of allergy showed reactions identical with those of the remaining infants. There was no significant change in the intensity of the reactions when the position of the tests on the back was varied. Often the reaction in the Negro infant was

* Eli Lilly and Co. product.

more difficult to interpret because of the lack of contrast between the reaction and the dark skin.

Twenty-six of the 27 older children revealed erythema flares in dilutions up to and including 1:512,000. The average diameter of the erythema was 2.6 cm. and wheal reactions were common in dilutions of 1:8000 and in a few instances in higher dilutions (table 2). Itching was severe when the higher concentrations were used. The erythema flares reached their height in about 10 minutes and disappeared in about 45 minutes.

2. Ability of the Skin of the Newborn Infant to Fix Antibody.

PROCEDURE

Newborn male and female infants, Negro and white, varying in age from several hours to 5 or 6 days, were selected at random. Serum from a ragweed sensitized patient, diluted serially from

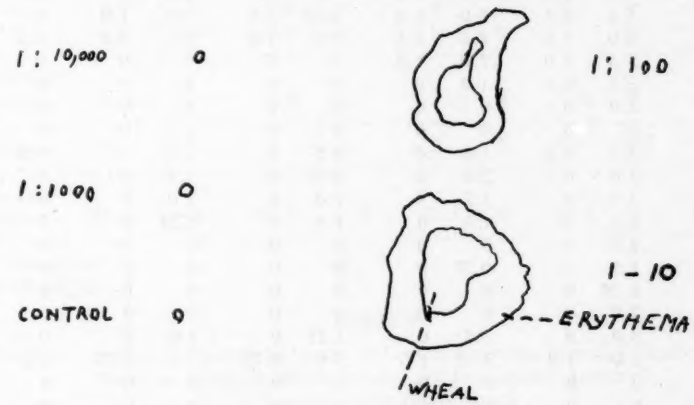


FIG. 3. Tracings of reactions in newborn infant obtained by passive transfer technic. Sites prepared with 0.05 cc. ragweed-sensitive serum and tested 24 hr. later with 0.05 cc. 1:100 dilution antigen.

1:10 to 1:10,000, was injected intradermally in .05 cc. amounts in a series of sites on the back. Twenty-four to 48 hr. later 0.05 cc. of a 1:100 dilution of ragweed antigen was introduced intradermally into each of the previously injected sites and the skin reaction, time of appearance, and size was noted. The size of the reaction was outlined, traced and recorded (Fig. 3). A second group of newborn infants were tested similarly using 0.1 cc. of the various dilutions of serum-containing ragweed reagin and 0.1 cc. of ragweed antigen in a 1:100 dilution. Ragweed antigen 1:100 was used as control.

A group of prematurely born infants varying from 6 to 74 days of age were selected. Their weights varied from 1500 to 1875 gm. The skin of these infants was prepared in a manner similar to that in the first series, except that a hen egg-sensitive serum was used, i.e., a human serum containing hen egg reagins. An intradermal injection of 0.05 cc. of the specific serum undiluted, and in dilutions of 1:10, 1:30, 1:90, and 1:270 was made into various sites on the back. Twenty-four hours later an intradermal injection of egg white protein in dilution of 1:10 was made into the respective sites and the reactions noted as to time of appearance, size and presence of wheal formation. Egg antigen 1:10 was used as control.

RESULTS

Tables 3 and 4 show the results of passive transfer studies in the newborn infants using ragweed reagin and antigen. Many of the infants demonstrated reactions, depend-

TABLE 3

PASSIVE TRANSFER TESTING OF NEWBORN INFANTS

0.05 cc. serum containing ragweed reagin was injected into skin sites and followed in 24 to 48 hr. by intradermal injection of 1:100 ragweed antigen into previously injected sites

Antiserum Dilution	1:10		1:100		1:1000		1:10,000		Control	
Case	E cm.	W cm.	E	W	E	W	E	W	E	W
1.	2.5	0	1.5	0	1.0	0	0.75	0	0.75	0
2.	3.0	1.5	0	0	0	0	0	0	0	0
3.	5.0	1.5	0	0	0	0	0	0	0	0
4.	6.0	2.0	2.5	1.0	4.5	1.5	1.0	0	0	0
5.	5.5	0.5	2.0	1.0	4.25	1.0	1.5	1.0	0.5	0
6.	6.0	1.0	2.5	1.5	3.0	1.0	3.0	1.5	0.5	0
7.	3.5	1.0	2.0	1.0	0	0	0	0	0	0
8.	2.5	0.5	1.0	0	0	0	0	0	0	0
9.	2.0	0.5	0	0	0	0	0	0	0	0
10.	0	0	0	0	0	0	0	0	0	0
11.	3.5	0.5	1.0	0	0.5	0	0.5	0	1.0	0
12.	3.0	0	2.0	0	0.75	0	0.5	0	0	0
13.	2.5	0	1.5	0	1.0	0	1.0	0	0	0
14.	3.5	0	1.5	0	1.5	0	1.25	0	0	0
15.	4.0	0	0	0	0	0	0	0	0	0
16.	1.5	0	0.75	0	0	0	0	0	0	0
17.	1.25	0	0	0	0	0	0	0	0	0
18.	2.0	0	0	0	0	0	0	0	0	0
19.	3.0	0	1.5	0	1.25	0	1.0	0	0	0
20.	5.0	1.0	3.75	1.0	3.0	0.75	2.5	0.75	1.5	0
21.	0	0	0	0	0	0	0	0	0	0
22.	0	0	0	0	0	0	0	0	0	0
23.	4.0	1.0	2.5	0.5	0	0	0	0	0	0
24.	2.5	0.75	0	0	0	0	0	0	0	0
Ave. Size Positives	3.42	1–	1.85	1.0	2.07	1.06	1.3	1.08	1–	0
Positive	21	12	14	6	10	4	10	3	5	0
Per Cent Positive	87.5	50	62.5	25	41.66	16.6	41.6	12.5	20.8	0

E —Erythema.
W—Whealing.

ing upon the dilution of the serum used in preparation of the skin site. In the case of the sites prepared with a 1:10 dilution of serum and using .05 cc. of both serum and antigen, 21 (86.5%) of the infants showed an erythema over 0.5 cm. in diameter and 12 of these (50%) demonstrated whealing. In 8 infants in whom the dosage of antigen and antibody was increased to 0.1 cc., 7 demonstrated a positive reaction with erythema and 6 with wheal formation. In the higher dilutions, scattered positive reactions occurred. Six of the controls showed erythema reactions up to 1.5 cm. The control erythemas

TABLE 4

PASSIVE TRANSFER TESTING OF NEWBORN INFANTS (CONTINUED)

0.1 cc. ragweed reagin dilution and 0.1 cc. ragweed antigen used

Antiserum Dilution	1:10		1:100		1:1000		1:10,000		Control	
Case	E	W	E	W	E	W	E	W	E	W
1.	3.5	0.75	1.5	1.0	0	0	0	0	0	0
2.	0	0	0	0	0	0	0	0	0	0
3.	1.25	0	1.5	0	1.25	0	2.0	0	0	0
4.	2.25	0.5	1.25	0	1.5	0	1.0	0	1.0	0
5.	2.25	0.75	2.25	0	0	0	0	0	0	0
6.	2.0	2.75	1.5	0.75	0	0	0	0	0	0
7.	2.0	0.5	1.0	0	0	0	0	0	0	0
8.	2.0	0.5	2.0	0	0	0	0	0	0	0
Ave. Size Positives	2.18	1–	1.57	1–	1.37	0	1.5	0	1.0	0
Positive	7	6	7	2	2	0	2	0	1	0
Per Cent Positive	87.5	75.0	87.5	25.0	25.0	0	25.0	0	1.25	0

E —Erythema.
W—Whealing.

TABLE 5

REACTIVITY OF SKIN OF PREMATURE INFANT BY PASSIVE TRANSFER TECHNIC UTILIZING EGG-SENSITIVE SERUM IN PREPARING SITES AND INTRADERMAL INJECTION OF EGG ANTIGEN 24 HOURS LATER

Case	Gest. Period (wk.)	Birth wt. (gm.)	Test wt. (gm.)	Age days	Serum Dilutions 1:10 E	1:10 W	1:30 E	1:30 W	1:90 E	1:90 W	1:270 E	1:270 W	React. Time Min.	Control
1	34	1225	1750	61	1.5	0.5	1.0	0	0	0	0	0	10	0
2	38	1550	1558	20	1.0	0.5	0	0	0	0	0	0	12	0
3		2010	1880	6	0	0	0	0	0	0	0	0		0
4		1925	1700	6	2.0	1.0	1.0	0.5	0	0	0	0	12	0
5	32	1515	1580	30	1.5	0.5	0	0	0	0	0	0	15	0
6	32	1445	1550	30	0	0	0	0	0	0	0	0		0
7	35	1770	1875	19			1.5	0.5	1.5	0.5	0	0	15	0
8	32	1500	1540	33	1.5	0.5	0	0	0	0	0	0	15	0
9	40	1500	1500	21	0	0	0	0	0	0	0	0		0
10	26	800	1600	74	1.0	0.5	0.5	0	0	0	0	0	20	0
11	32	1455	1675	51	2.0	1.0	1.0	0.5	1.0	0.5	0	0	12	0
12	33	1735		17	2.0	1.0	1.5	1.0	1.5	0.5	0	0	12	0
			Tested		11	11	12	12	12	12	12	12	Ave. React.	
			Positive		8	8	6	4	3	3	0	0	Time—13.7	
			% Positive		73	73	50	33	25	25	0	0		
			Average Size Positives		1.5	0.7	1.1	0.6	1.3	0.5				

E —Erythema.
W—Wheal.
Control—egg white 1:10 intradermally.

TABLE 6

Indirect Skin Testing in Newborn Infants

Reactions in skin sites previously sensitized by intradermal injection of varying dilutions of egg-sensitive serum to feeding of egg white 24 hr. later

Serum Dilution	Undiluted		1:10		1:100		1:1000		Control	
Case	E cm.	W cm.	E	W	E	W	E	W*	E*	W*
1.	1.0	0.25n	*	*	*	*	*			
2.	0.75	0.25n	0.75	0.25n	*	*	*			
3.	*	*	*	*	*	*	*			
4.	*	*	*	*	*	*	*			
5.	5.5	2.0	1.5	*	*	*	*			
6.	2.0	*	1.0	*	*	*	*			
7.	2.0	1.0	*	*	*	*	*			
8.	3.0	1.5	*	*	*	*	*			
9.	3.5	1.5	1.0	1.0	*	*	*			
10.	2.0	1.0	1.5	1.0	1.0	*	1.0			
11.	1.5	1.0	1.0	0.5	1.0	*	*			
12.	1.5	0.5	1.0	*	*	*	*			
13.	3.0	*	2.5	*	2.0	*	*			
14.	2.5	0.5	1.0	*	0.5	*	*			
15.	7.0	3.0	4.5	*	*	*	*			
16.	2.0	1.0	0.5	*	0.5	*	*			
17.	5.5	2.5	1.0	*	0.5	*	*			
18.	4.0	1.5	0.5	*	*	*	*			
19.	4.0	2.0	1.0	*	*	*	*			
20.	*	*	*	*	*	*	*			
21.	4.5	3.0	2.0	1.5	*	*	*			
22.	*	*	*	*	*	*	*			
23.	*	*	*	*	*	*	*			
24.	4.5	2.5	2.5	1.0	1.0	*	*			
25.	*	*	*	*	*	*	*			
26.	*	*	*	*	*	*	*			
27.	*	*	*	*	*	*	*			
28.	2.0	*	1.0	*	*	*	*			
29.	1.0	*	0.5	*	*	*	*			
30.	5.5	3.5	2.5	1.0	1.0	1.0	*			
31.	3.5	3.0	5.0	4.5	1.5	*	*			
32.	5.5	3.0	2.0	*	1.0	*	*			
33.	1.5	*	1.0	*	1.0	*	*			
34.	*	*	*	*	*	*	*			
35.	4.5	2.0	3.0	1.0	3.0	1.0	*			
Tested	35									
Positive	26	19	23	8	12	2	1	0	0	0
Per Cent Positive	74	54	66	23	34	5.6	3			
Ave. Size Positive	3.2	1.9	1.7	1.4	1.2	1.0	1.0			

* No reaction observed.
Control = Normal saline.
E = Erythema.
W = Whealing.

disappeared in approximately 15 minutes as contrasted to 45 minutes' disappearance time for the erythemas resulting from the antigen-antibody union.

Eight of the 11 premature infants, whose skin had been prepared with 1:10 dilution of serum containing reagin to egg and tested 24 hours later with 1:10 dilution of egg antigen, showed positive reactions. Whealing was present in all 8. In general, the size of the reaction was small in the premature infants. Though no comparison can be made with the full term infant, in whom a different antigen was used, the skin reactions were easily demonstrable. Controls with egg white antigen were negative in all cases (table 5).

3. Demonstration of Reaction in Passively Sensitized Sites Following Ingestion of the Specific Antigen.

PROCEDURE

Hen egg protein was selected as a testing antigen because it is considered a frequent offending agent in allergic manifestations in infancy. Normal full term infants varying in age from 18 hr. to 6 days, of both sexes, white and Negro, were selected at random. Skin sites on the back were sensitized in a manner previously described by injecting 0.1 cc. of a potent reaginic serum from an egg-sensitive individual. Serial dilutions varying from 1:10 to 1:1000 were used intradermally. After 24 hr. had elapsed, 4 cc. of whole raw egg was fed by dropper midway between the regular milk formula feedings. The few breast-fed infants in this series were tested on the first day of life before breast feeding was instituted. Reactions were observed immediately after feeding and recorded by measurement and sketch as described above.

For comparison a group of older children were selected and similarly tested. These were preschool and school age patients of both sexes, white and Negro, hospitalized for surgical, orthopedic or ear, nose and throat conditions. They were placed on an egg-free diet for 36 hr. before testing. Twenty-four hours after preparation of local skin sites, they were fed up to 4 to 5 teaspoons of whole egg and the reactions observed.

RESULTS

The results are shown in table 6 and fig. 4. Of 35 newborn infants sensitized by intradermal injections of serum with egg reagin and fed whole egg 24 hours later, positive erythema reactions at the injection sites occurred in 26 (74%) and typical wheal formation in 19 (54%). The average size of the erythema flare was 3.2 cm. and of the wheal 1.9 cm. In the case of the sites prepared by varying dilutions of the specific serum, the

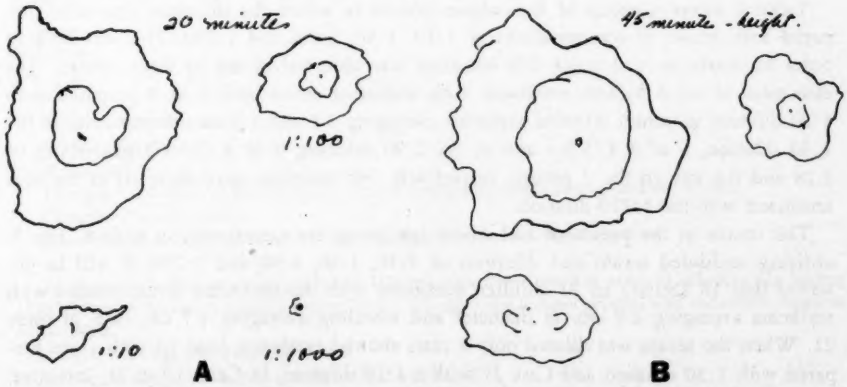


FIG. 4. Tracings of reactions obtained in passively sensitized sites of newborn infant after feeding of egg 24 hr. later. A. Reaction 20 min. following feeding. B. Reaction at height 45 min. following feeding.

TABLE 7

EXPERIMENT SHOWN IN TABLE 6 REPEATED USING DIFFERENT DILUTIONS OF EGG-SENSITIZED SERUM TO PREPARE SITES

Serum Dilution	Undiluted		1:10		1:30		1:90		1:270		Control	
Case	E	W*	E	W*	E	W*	E	W*	E*	W*	E*	W*
1.	1.5				1.0		*					
2.	2.0				*		*					
3.	2.0				1.0		0.5					
4.	3.0				2.0		*					
5.			*		*		*					
6.			2.5		2.0		1.0					
7.			1.0		0.75		*					
8.			2.0		1.0		0.5					
Tested	4	4	4	4	8	8	8	8	8	8	8	8
Positive	4	0	3	0	6	0	3	0	0	0	0	0
Per Cent	100	0	75	0	75	0	33	0	0	0	0	0
Average Size Pos.	2.1		1.8		1.28		0.6					

* No reaction observed.
E —Erythema.
W—Whealing.

number of positive reactions and their size diminished as the dilutions were increased. Using the 1:10 dilution, 23 (66%) revealed erythema averaging 1.7 cm. in diameter and 8 (23%) wheal formation averaging 1.4 cm. With a 1:100 dilution of serum 12 (34%) showed erythema averaging 1.2 cm. and 2 (5.6%) showed wheals of 1 cm. With a 1:1000 dilution of serum, only one case showed an erythema of 1 cm. and no wheals were observed.

Table 7 shows a group of 8 newborn infants in whom the injection sites were prepared with serum in concentrations of 1:10, 1:30, 1:90, and 1:270. This was done in order to obtain an end point. No whealing was observed in any of these infants. The skin sites of all 4 infants sensitized with undiluted serum and 3 of 4 prepared with 1:10 dilution of serum revealed erythema averaging 2.1 and 1.8 cm., respectively. In the 1:30 dilution, 6 of 8 (75%) and in the 1:90 dilution, 3 of 8 (35%) gave flares of 1.28 and 0.6 cm. in the 2 groups, respectively. No reactions were obtained in the sites sensitized with the 1:270 dilution.

The results in the preschool and school age group are summarized in table 8, Fig. 5, utilizing undiluted serum and dilutions of 1:10, 1:30, 1:90 and 1:270. It will be observed that 18 (89%) of 21 children sensitized with the undiluted serum reacted with erythema averaging 2.9 cm. in diameter and whealing averaging 1.7 cm. in 7 of these 21. When the serum was diluted only 2 cases showed erythema, Case 14 with a site prepared with 1:30 dilution and Case 17 with a 1:10 dilution. In Cases 17 to 21, inclusive, the site prepared with a 1:90 dilution of serum was tested intradermally with a 1:10 egg white antigen solution after having failed to respond to the egg feeding. All 5 of these children responded with an immediate and well defined erythema.

TABLE 8

INDIRECT SKIN TESTING IN GROUP OF OLDER CHILDREN SUMMARIZING REACTIONS OBTAINED IN SKIN SITES SENSITIZED BY INTRADERMAL INJECTION OF EGG-SENSITIVE SERUM FOLLOWED IN 24 TO 48 HOURS BY EGG FEEDING

Serum Dilution	Undiluted		1:10		1:30		1:90		1:270		Control	
Case	E	W	E	W*	E	W*	E*	W*	E*	W*	E*	W*
1.	2.0	*			*							
2.	2.0	*			*							
3.	9.0	1.0	*		*							
4.	2.0	*	*		*							
5.	1.0	*	*		*							
6.	8.0	5.0	*		*							
7.	4.0	2.0	*		*							
8.	*	*	*		*							
9.	2.0	1.0	*		*							
10.	1.0	*	*		*							
11.	1.0	*	*		*							
12.	1.0	*	*		*							
13.	1.0	*	*		*							
14.	2.0	*			1.0							
15.	*	*	*		*							
16.	*	*	*		*							
17.†	4.0	1.0	1.0		*							
18.‡	3.0	1.0	*		*							
19.§	3.0	0.5	*		*							
20.‖	3.5	*	*		*							
21.¶	3.0	0.5	*		*							
Tested	21	21	18	18	21	21	21	21	21	21	21	21
Positive	18	7	1	0	1	0	0	0	0	0	0	0
Per Cent Positive	89	33	6	0	5							
Average Size Positive (cm.)	2.9	1.7										

* No reaction observed.
E = Erythema.
W = Wheal.
Dilution = Dilutions of known human serum containing antibodies against egg protein.
Control = Normal saline.
Reactions measuring less than 0.5 cm. in diameter were considered negative.

In Cases 17 to 21, one of the previously injected sites which failed to respond following egg feeding (1:90) when subjected to direct injection with 1:10 egg white antigen produced an immediate response as recorded.

† After 1:10 egg white injection—3.0 0.
‡ After 1:10 egg white injection into negative site—2.0 0.
§ After 1:10 egg white injection into negative site—3.0 0.
‖ After 1:10 egg white injection into negative site—3.0 0.5.
¶ After 1:10 egg white injection into negative site—3.0 0.

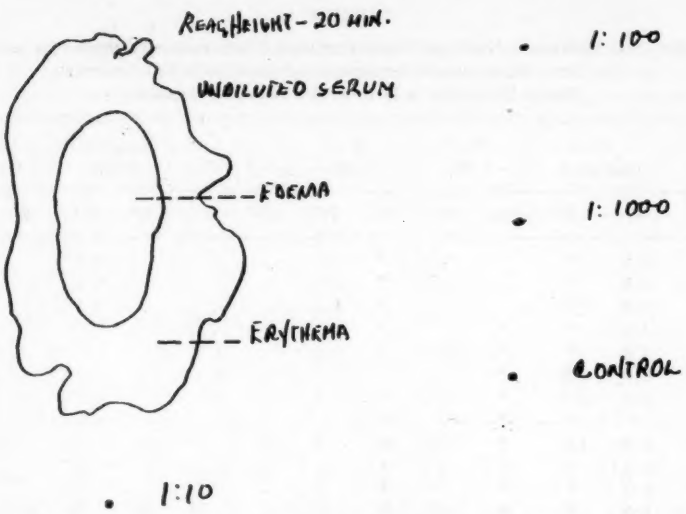


FIG. 5. Tracing of reactions after egg feeding obtained in older child 24 hr. after passive sensitization of skin sites with dilutions of reaginic serums. Reaction at its height in 20 min.

The reaction time, i.e., the length of time from the feeding to the beginning reaction in the skin, averaged 30 minutes in the newborn infant and 22.7 minutes in the older children. In both series, sites prepared by injection with diluted antiserum which had not reacted to egg feedings were tested by the intradermal injection in situ of a 1:100 dilution of egg antigen. In every case there was a rapid, well defined, local reaction in the form of erythema and wheal formation of varying intensity.

In order to demonstrate the local desensitizing effect in the sites prepared with specific serum by the initial feeding of egg, refeeding was carried out at 24, 48 and 72 hours in five newborn infants. Table 9 gives the results in these infants. It will be noted that in no instance was there a reaction similar to the one obtained at 24 hours. In one case a minimal erythema response of 0.5 cm. was observed at 48 hours.

4. Skin Reaction in Passively Sensitized Areas Following Subcutaneous Injection of the Antigen.

PROCEDURE

This experiment was devised to compare the reactivity of the skin to the antigen introduced by way of the gastrointestinal tract with that produced by protein introduced parenterally. As in the preceding group, the skin of the newborn infants was prepared by the intradermal injection of specific egg-sensitive serum in graded dilution. Twenty-four hours later a peripheral subcutaneous injection of egg white in 1:100 dilution produced no reactions in any of the prepared sites. The experiment was then repeated using subcutaneous injection of 1:10 dilution of egg white in dosages of 0.05 to 0.1 cc. into similar peripheral sites. The results are shown in table 10. In all 10 infants the sites prepared with undiluted serum revealed reaction to the peripheral subcutaneous injection of egg white with erythema and wheal formation. The reactions were clearcut, revealing an average erythema diameter of 3.75 cm. and an average wheal diameter of 2.35 cm. In the instances where the sites were prepared with 1:10 serum dilution, 2 cases exhibited both erythema and wheal formation in response to subcutaneous peripheral egg white injection. The average reaction time in this experiment was 14 minutes in comparison with 30 minutes in the egg ingestion series. In

TABLE 9

REACTIONS OF SENSITIZED SITES TO EGG FEEDINGS AT 24 HOUR INTERVALS IN 5 NEWBORN INFANTS

Serum Dilution		Undiluted		1:10		1:100		1:1000		Control	
Case	Feeding hours	E cm.	W cm.	E	W	E*	W*	E*	W*	E*	W*
1.	24	5.0	2.0	1.0	*						
	48	*	*	*	*						
	72	*	*	*	*						
	96	*	*	*	*						
	120	*	*	*	*						
2.	24	2.0	*	*	*						
	48	*	*	*	*						
	72	*	*	*	*						
	96	*	*	*	*						
	120	*	*	*	*						
3.	24	3.0	1.0	*	*						
	48	*	*	*	*						
	72	*	*	*	*						
	96	*	*	*	*						
	120	*	*	*	*						
4.	24	3.5	2.0	1.0	*						
	48	0.5	*	*	*						
	72	*	*	*	*						
	96	*	*	*	*						
	120	*	*	*	*						
5.	24	7.0	3.0	4.5	2.0						
	48	*	*	*	*						
	72	*	*	*	*						
	96	*	*	*	*						
	120	*	*	*	*						

* No reaction observed.
E = Erythema.
W—Whealing.
Total cases tested—5.
No. positive at 48 hr.—1 (Case 4).
No. positive after 48 hr.—0.

every instance those sites prepared with 1:10 and 1:100 dilutions of serum which failed to react to peripheral injection of egg white, exhibited strong positive reactions when injected directly with 1:10 egg white antigen.

COMMENT

The response of the skin of the newborn infants to histamine with erythema and without whealing, as contrasted to its consistent wheal response to antigens applied to passively sensitized sites, is difficult to understand. It is to be noted, however, that the

TABLE 10

REACTIONS IN PASSIVELY SENSITIZED SKIN AREAS TO SUBCUTANEOUS INJECTION OF 1:10 EGG WHITE

Serum Dilution	Undiluted		1:10		1:100		1:1000		Control	
Case	E cm.	W cm.	E	W	E*	W*	E*	W*	E*	W*
1.	3.0	1.5	*	*						
2.	4.5	2.5	*	*						
3.	3.0	2.5	*	*						
4.	2.5	1.0	*	*						
5.	5.0	3.0	*	*						
6.	2.5	1.0	*	*						
7.	3.5	2.5	*	*						
8.	3.5	2.5	*	*						
9.	6.0	3.5	3.0	0.5						
10.	4.0	3.5	2.0	1.0						
Total	(using 1:10 egg white antigen for peripheral injection)									
Tested	10	10	10	10	10	10				
Positive	10	10	2	2	0	0				
Per Cent Positive	100	100	20	20	0	0				
Ave. Size Positives	3.75	2.35	2.5	0.75						

* No reaction observed.
E —Erythema.
W—Whealing.
Control—Normal saline.
Reaction less than 0.5 cm. diameter considered negative.
Reaction time average—14 min.
Note: Areas containing serum of 1:10 and 1:100 dilutions which did not react to peripheral injection became strongly positive following direct injection of 1:10 egg white antigen.

testing with histamine involved scratch technic while testing in passively sensitized sites involved intradermal technic. The reason usually proposed for the failure of the skin of newborn infants to form wheals is its anatomic or structural difference from that of the older child. In view of these investigations, this explanation does not appear valid.

The experiments involving the ingestion of egg afforded an opportunity to study the absorption of protein from the gastrointestinal tract in a series of newborn infants. A brief review of similar observations involving experimental animals and older humans may be of interest.

Ganghofner and Langer[13] found that the intestinal tract of young animals permitted the passage of heterologous protein (beef and egg) as determined by precipitin tests in the blood serum. In the usual average feeding amounts, however, this occurred only in animals less than eight days old. Meyerhofer and Pribam[14] observed increased permeability of the gastrointestinal tract in infants in the presence of acute enteritis. Schloss, Anderson and Myers,[15] using precipitin technic, concluded that the gastrointestinal tract of the normal infant is capable of absorbing antigenic protein.

Ratner and Gruehl,[16] in a series of experiments utilizing both animals and humans, came to the conclusion that complete proteins were absorbed by the intact gastrointestinal tract much more frequently than previously supposed. They found that mature as well as young animals could be sensitized and shocked by the oral administration of protein foods. The incidence in a large series of animals was shown to be as high as 50%. In the human they found that proteins, natural as well as foreign to the diet, enter the blood stream in infants of all ages. In this connection an experiment by Vahlquist and Hgstedt[17] is of interest. They studied the absorption of antibodies, which according to modern concepts are usually gamma globulins. They fed human serum rich in diphtheria antibodies to newborn infants between 12 and 24 hours of age, and continued the feeding for 3 or 4 days. All the infants accepted for study had no measurable antitoxin in their blood. It was found that with few exceptions, an absorption of antibodies could be traced only in the first week of life and then, in only minute amounts—less than 0.30% of the total antibody administered.

The authors' foregoing experiments indicate that protein digestive products of sufficient complexity to be antigenic may be absorbed from the digestive tract by the young human, not only in the newborn period, but in the older child as well. This data cannot be interpreted as signifying that such protein is absorbed in unaltered form. It was possible to obtain definite wheal formation in the sensitized sites of 54% of newborn infants fed egg white. In the school age and preschool group 89% revealed erythema and wheal formation in sites prepared with undiluted serum and egg white fed 24 hours later. Furthermore, Pseudopodia were frequently noted in the wheals formed on the skins of both newborn infants and older children in the higher serum concentration sites. Also the reaction time was more rapid in the older group. It is possible that altered gastric acidity and secretions in the newborns is one of the factors to account for this slower reaction time. It is known that on the first day of life the gastric acidity is relatively high, between 15 and 20 cc. of free N/10 HCl./100 cc. of gastric juice. This is temporary and acidity rapidly decreases so that on the seventh day of life there may be very little free acid. Walzer[18] has shown that gastric hypoacidity increased the absorption rate of proteins from the gastrointestinal tract whereas hyperacidity retarded absorption.

Although the average reaction time in the newborn infants who were fed egg was 30 minutes and in the older children about 22 minutes, there were many individual instances in both groups where evidence of absorption of such protein products was present as early as 5 to 7 minutes after ingestion.

Summary

The skin of the full term newborn infant reacts to various dilutions of histamine phosphate with erythema but no wheal formation, as contrasted to the skin of older children where, with the same technic (scratch), whealing was frequent.

The skin of the full term newborn infant is capable of fixing reagin locally.

Similar fixation of antibody (and skin reactions with tendency to smaller wheals) was shown in prematurely born infants of varying ages and weight.

The skin sites passively sensitized with serum containing reagin to egg showed erythema and whealing following the feeding of whole raw egg to both newborn infants and older children. This suggests that proteins or products of protein digestion, of sufficient complexity to be antigenic, are absorbed from the gastrointestinal tract of both newborn infants and older children.

The above experiments support the view that the skin of the newborn infant is capable of demonstrating an antigen antibody reaction and that such reaction may be in the nature of erythema or whealing.

ACKNOWLEDGMENT

The authors are greatly indebted to Dr. Samuel M. Feinberg for his valuable aid in the planning of these experiments.

REFERENCES

1. Adelsberger, L., Das Verhalten der kinderlichen Haut gegenüber verschiedenen Reizen, Ztschr. f. Kinderh. **43**:373, 1927.
2. Friedberger, E., and Heim, F., Zur Deutung der negativen Schickschen Reaction, insbesondere bei Säuglingen, Deutsche med. Wchnschr. **55**:132, 1929.
3. Ruh, H. D., and McClelland, J. E., Comparison of diphtheria immunity in mothers and in newborn, Am. J. Dis. Child. **25**:59, 1923.
4. Cooke, J. V., Relation between antitoxin in blood and skin sensitivity in newborns and their mothers, Am. J. Dis. Child. **34**:369, 1927.
5. Kobak, A. J., and Pilot, I., Skin reactivity of mothers and infants to Staphylococcus aureus filtrate and vaccine, Proc. Soc. Exper. Biol. & Med. **28**:584, 1931.
6. Kobak, A. J., and Greengard, J., Skin reactivity of mothers and infants to gonococcus vaccines, Proc. Soc. Exper. Biol. & Med. **30**:117, 1932.
7. Balyeat, R. M., Hereditary factor in allergic disease, Am. J. M. Sc. **176**:1332, 1928.
8. Coca, A., Walzer, M., and Thommen, A., Asthma and hay fever in theory and practice, Springfield, Ill., Charles C Thomas, Publisher, 1931, p. 327.
9. Zohn, B., Skin testing in newborn, Arch. Pediat. **58**:339, 1941.
10. Smyth, F. S., and Bain, K., Direct skin test in allergy, J. Allergy **2**:316, 1931.
11. Carey, T. N., and Gay, L. N., Skin reactions in infants: Susceptibility and passive atopic sensitization, J. Allergy **5**:488, 1933-34.
12. Sulzberger, M., and Baer, R., Whealing capacity of skin of newborn or young infants, Arch. Dermat. & Syph. **41**:1029, 1940.
13. Ganghofner, F., and Langer, J., Ueber die Resorption genuiner Eiweisskörper im Magendarmkanal neugeborenen Tiere and Säuglinge, München. med. Wchnschr. **51**:1497, 1904.
14. Meyerhofer, E., and Pribam, E., Ueber die Beeinflussung der Diffusionsvorgänge an frischen tierischen Darmmembraner, Biochem. Ztschr. **24**:453, 1910.
15. Schloss, O. M., Anderson, A. F., and Myers, C., Intestinal absorption of antigenic protein by normal infants, Proc. Soc. Exper. Biol. & Med. **23**:180, 1925.
16. Ratner, B., and Gruehl, H. L., Passage of native proteins through normal gastro-intestinal wall, J. Clin. Investigation **13**:517, 1934.
17. Vahlquist, B., and Hgstedt, C., Minute adsorption of diphtheritic antibodies from gastro-intestinal tract of infants, PEDIATRICS **4**:401, 1949.
18. Walzer, M., Immunology review, J. Allergy **7**:600, 1935.

SPANISH ABSTRACT

Reactividad de la Piel de los Niños Recién Nacidos

La piel del niño recién nacido es capaz de reaccionar a los irritantes dérmicos o a antígenos específicos?. Es capaz de desarrollar reacciones papulosas como la piel de los niños mas grandes y adultos?. En vista de los reportes contradictorios y confusos en la literatura, se pensó hacer un intento para aclarar este punto y se llevaron a cabo las siguientes investigaciones.

1. Cutirreacciones en recién nacidos y en niños mayores con diluciones seriadas de histamina y comparación de los resultados de ambos grupos.

2. Fijación de reagina por la piel de niños recién nacidos, a término y prematuros.

3. Demostración de reacciones cutáneas, en sitios sensibilizados pasivamente, después de la ingestión del antígeno específico y comparación de los resultados obtenidos con la misma técnica en niños mayores.

4. Demostración de reacciones cutáneas en recién nacidos, en sitios sensibilizados pasivamente, después de la inyección subcutánea del antígeno específico.

Como resultado de los experimentos arriba mencionados se llegó a las siguientes conclusiones:

1. La piel del niño recién nacido reacciona, a diferentes diluciones de histamina, con eritema, pero sin formación de pápula, contrastanto con la piel de niños mayores en quienes sí la hubo frecuentemente, usando técnicas iguales (rasguño) para ambos grupos.

2. La piel del niño recién nacido es capaz de fijar reagina.

3. Fijación similar de reagina y reacciones dérmicas con menor tendencia a formación de pápula se demostró en niños nacidos prematuramente.

4. Los sitios de la piel previamente sensibilizados con suero que contenía reagina al huevo mostraron eritema y pápula después de dar huevo crudo completo tanto en niños recién nacidos como en niños mayores. Esto sugiere que las proteínas o productos de la digestión protéica de complexidad suficiente para ser antigénicos son absorvidos del aparato gastrointestinal tanto de recién nacidos como de niños mayores.

5. Los sitios de la piel que habían fijado reagina de huevo que no reaccionaron a la ingestión de huevo, respondieron rápidamente con eritema y pápula después de la inyección subcutánea periférica de proteína de huevo.

6. Estos experimentos sostienen el punto de vista de que la piel del niño recién nacido es capaz de demostrar una reacción antígeno-anticuerpo y que dicha reacción puede ser bajo la forma de eritema o pápula.

30 North Michigan Avenue

COMBINED PELVIC AND RETROPERITONEAL TERATOMAS IN INFANCY AND CHILDHOOD

By ERNEST E. ARNHEIM, M.D.
New York City

THE most common teratomas in infants and children have been located in the sacrococcygeal region. Reviews of reported cases have been contributed by Chaffin[1] and Ravitch and Smith.[2] Gross, Clatworthy and Meeker[3] stated that they were able to collect reports of 426 cases, and gave an excellent account of 40 cases treated at the Children's Hospital, Boston. The retroperitoneal area is a less common site of teratomas in infancy and childhood, 41 cases having been recorded (Arnheim).[4] There is a group of teratomas in this age group which occupies the pelvic (presacral) and retroperitoneal regions, and in some cases the perineum and buttocks. These children present special problems in surgical management, and when untreated they have died either of pressure effects on neighboring structures or of malignant degeneration. Fourteen examples of combined pelvic and retroperitoneal teratomas have been recorded in the literature.[3, 5-14]

PATHOLOGIC FEATURES

Combined pelvic and retroperitoneal teratomas are large cystic and solid tumors which arise in the presacral region and extend upward into retroperitoneal tissues. In some cases their growth is postero-inferiorly, presenting as a mass in one or both buttocks or extending downward between the lower extremities. The pelvic component of the tumor is bounded anteriorly by the rectum and posteriorly by the sacrum and coccyx. Its large size produces pressure upon the rectum in the pelvis, and the bladder and ureters in the retroperitoneal area. These tumors almost always have an attachment to the coccyx and sacrum.

Teratomas contain representatives of many embryonal elements—ectoderm, entoderm and mesoderm—with no evidence of orderly delamination.[15] Almost all teratomas are tridermal and component tissues are adult or embryonic, mature or immature. The most benign teratomas consist of fully mature tissues with no sign of proliferative activity; the most malignant ones contain abundant immature embryonic tissues. The incidence of malignancy in sacrococcygeal teratomas in infants and children has been recorded as 9%,[1] 17%[2] and 27.5%,[3] and in retroperitoneal teratomas in this age group as 6.8%.[4] In reviewing cases with combined pelvic and retroperitoneal teratomas the incidence of malignancy has been high—5 of 13 cases (38%) in which pathologic examination was recorded. These were malignant tumors of epithelial origin—papillary adenocarcinoma—with metastases to liver, lungs, retroperitoneal and bronchial lymph nodes in three cases.

CLINICAL FEATURES

The ages of the patients were as follows:

From the Departments of Surgery and Pediatrics, the Mount Sinai Hospital, New York City.
(Received for publication March 10, 1951.)

Cases	Age
9	0 to 1 yr. (3 in neonatal period)
2	1 to 2 yr.
2	2 to 5 yr.
2	not recorded

Both sexes were represented: 8 females, 5 males and 2 not recorded.

The clinical manifestations of these tumors varied with the anatomic location of the mass, presenting either partly as an external growth in the sacrococcygeal region (10 cases), or in the pelvis and lower abdomen alone (5 cases); in either location rectal and abdominal examinations detected the tumor. Diagnosis was made earlier in the former group. Symptoms were the result of pressure incident to the size of the tumor, or of metastatic spread. Urinary or intestinal obstruction were noted in 10 patients due to pressure on the bladder and ureters or rectum. Catheterization of the bladder was necessary to determine the degree of urinary retention and enable the examiner to palpate the retroperitoneal mass.

Plain roentgenograms in 4 cases revealed areas of density in the region of the tumors with calcifications in 3 and well formed bones in 1. Osseous changes in the sacrum and coccyx were not noted. In 3 patients intravenous pyelograms showed hydroureter, hydronephrosis, and vesical enlargement in 2, and displacement of the bladder and ureters in 1. A complete study should include roentgenologic examination of the lungs in view of the frequency of pulmonary metastases in malignant cases.

Differential Diagnosis

A myelomeningocele may present in the presacral region as a herniation of the meninges through a defect in the sacrum, resulting from failure of fusion of the laminae. Ingraham[16] reported 46 sacral myelomeningoceles in a series of 546 cases of spina bifida and cranium bifidum. A rare type of sacral spina bifida associated with an intrapelvic meningocele and sacrococcygeal teratoma in an infant has been recorded.[17] The usual myelomeningocele is located in the lumbar region, has no solid elements, is covered by a translucent membrane, varies in size with changes in cerebrospinal fluid pressure, is associated with abnormal neurologic signs in the lower extremities, and has roentgenologic evidences of spina bifida.

A variety of osseous and neurogenic tumors of the sacrococcygeal region have been described in adults, but these have rarely been noted in children. Three cases of sacrococcygeal chordoma have been recorded in infants;[18] these were in the presacral region, and involved the buttocks in two cases. The most important diagnostic aid in differentiating teratomas from chordomas in this region is roentgenologic examination —destructive osseous changes of the sacrum in chordomas are absent in teratomas, except in a few with malignant degeneration.

Ependymomas are rare in the sacral region; they originate from ependymal cells which line the central canal of the cauda equina, and are associated with nerve root changes.

A combined pelvic and retroperitoneal neuroblastoma in an infant treated by the author had the clinical features of a teratoma, which was the preoperative diagnosis.

Treatment and Results

Early and complete excision of combined pelvic and retroperitoneal teratomas is

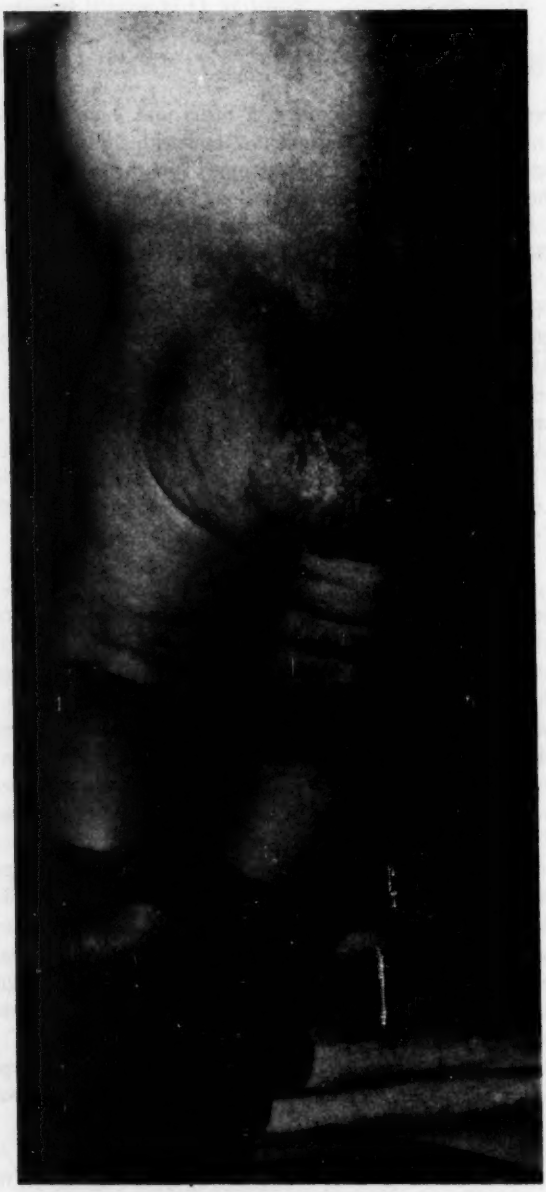


FIG. 1. Tumor in sacrococcygeal and gluteal region at 2 mo. of age, before operation.

necessary because of pressure changes and the high incidence of malignant degeneration. Removal necessitates a staged posterior (transpelvic) and abdominal (transperitoneal) approach. This combined procedure was carried out in four cases[3, 5, 6] and by the author in the case reported. A complete description of the technic of the transpelvic operation has been outlined by Gross, Clatworthy and Meeker[3] who emphasized the necessity of excising the coccyx with the neoplasm; in the author's case the lower sacral segment was also excised. These operations are attended by shock and hemorrhage, and adequate amounts of blood must be administered during and after operation. As evidence of the large amount of blood required, the infant to be reported, aged 2 months, received a total of 450 cc. blood during operation and the first postoperative day. Roentgen irradiation was not beneficial in two cases with adenocarcinoma.

Four cases of combined pelvic and retroperitoneal teratoma were untreated; 3 died in the neonatal period, and 1 at 9 months of age; the tumors were benign on pathologic examination. One child with a papillary adenocarcinoma was treated by roentgen irradiation and died at the age of 17 months. Of the 10 patients operated upon, 2 died early in the postoperative period (operative mortality 20%), and 1 each 2, 8 and 15 months after operation. On pathologic examination, 2 of these neoplasms were benign and 3 were malignant; supplementary roentgen irradiation was employed in 1 of the latter group. Two children recovered after operation and remained well—1, 3 years after removal of a benign neoplasm,[5] and 1, 4 4/12 years after excision of a partly malignant tumor (author's case). Follow-up information is not available after 3 other operative recoveries.

Case Report

History: A white female infant, aged 2 mo., was admitted to the Mount Sinai Hospital because of a mass in the gluteal region which had been present since birth. The patient had been a full term, normal delivery with birth weight of 2,890 gm. Pregnancy was uncomplicated except for a respiratory infection during the seventh month. Examination at birth revealed a tumor occupying both gluteal regions. RGs of the abdomen and pelvis, at 10 days of age, showed a mass filling the pelvis and lower abdomen, containing some areas of ossification. Irradiation was given (dose not stated). There were no urinary or intestinal symptoms. The mass was noted to have increased in size since birth. Family history seemed irrelevant.

Physical Examination: On admission examination revealed a well developed and well nourished infant. Her temperature was 37.5°C., and she weighed 4,678 gm. There were no abnormalities about the head, heart, lungs, extremities or genitalia.

A hard, nodular, nontender mass filled most of the lower part of the abdomen to the level of the umbilicus; the right side of the mass was larger than the left. The liver, spleen and kidneys were not palpable.

A large mass projected from the sacrococcygeal region; it extended into both gluteal regions across the intergluteal fold (Fig. 1). The tumor felt partly cystic and partly solid, and measured about 7 x 5 cm. in diameter. There was a slight bluish discoloration and a few dilated veins in the skin covering the mass. On rectal examination, the right lateral and posterior walls were compressed by a firm, smooth mass.

Laboratory Data: On admission Hgb. was 13.5 gm./100 cc.; WBC 5.6 thousand/cmm. with 35% polymorphonuclear leukocytes, 62% lymphocytes, 2% eosinophils and 1% monocytes. Urinalysis was normal.

Roentgenograms: RGs of the chest and long bones were normal. RG of the abdomen and pelvis showed a large mass occupying the lower abdomen and pelvis, extending below and posterior to the coccyx; loops of small intestine were displaced upward and anteriorly; a few irregular areas of calcification were seen within the mass; no abnormalities were noted in the pelvic bones or spine.

Operation: Operation was performed 2 days after admission. Under ether anesthesia, an

encapsulated tumor was found to occupy the entire right gluteal region, crossing the midline into the left gluteal area. On its deep surface the tumor lay anterior to the sacrum and coccyx and entered the pelvis. The tumor was adherent to the coccyx and lower sacral segment. The pelvic portion of the tumor was crowded between the sacrum and the rectum.

The neoplasm was excised from the gluteal region, followed by removal of the coccyx and lower sacral segment. The pelvic fascia and levator ani muscles were divided. Dissection around the tumor was continued upward into the pelvis. It was obvious that the pelvic portion of the tumor was a downward extension of a retroperitoneal tumor. When the upward limit of dissection was reached, the tumor was transected. A cyst was entered, with the escape of odorless milk-like fluid. The cut end of the tumor was partially closed with a suture of tantalum wire to control oozing and to help in future identification. Sulfanilamide powder was scattered over this

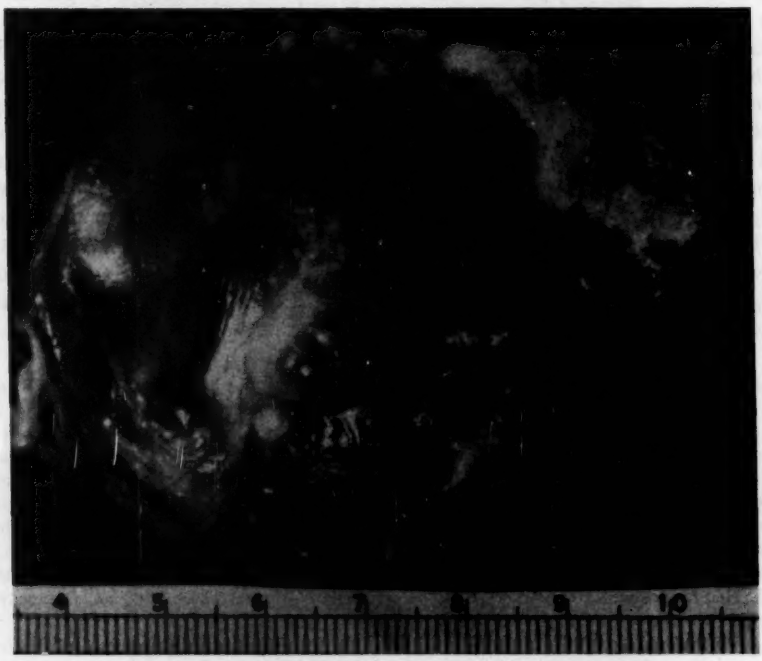


FIG. 2. Operative specimen showing cystic and solid structure of tumor.

area, and a packing was inserted into the pelvis. The large space in the gluteal region formerly occupied by the tumor was obliterated with pressure dressings after closure of the skin.

Report of Pathology: The specimen was an encapsulated tumor which measured about 7 x 5 x 5 cm. in diameter (Fig. 2). The surface was smooth, pink in color, and contained many yellow nodules, about 8 mm. in diameter, which on section contained greenish mucoid material. Section of the tumor revealed a nodular, pinkish-grey tissue and many cystic areas containing clear fluid.

On microscopic examination, the tumor was found to consist of mature tissues in some areas—cartilage, bone, and cystic areas lined by ciliated epithelium (Fig. 3), and mitotic figures in others.

Course: An intravenous infusion of 5% dextrose in saline and 100 cc. of citrated blood were given during the operation. A state of severe shock was noted 1½ hr. after operation, as manifested by pallor, dyspnea, and a rapid pulse of small volume; RBC 1.67 million/cmm. and Hgb. 4 gm./100 cc. There was no bleeding from the wound. Oxygen was supplied, and 150 cc. citrated blood was rapidly administered. The color and the quality of the pulse improved, but

the respirations continued rapid and slightly labored. Blood was noted on the dressing during the transfusion. Twenty hours after operation RBC was 1.7 million/cmm. and Hgb. 4 gm./100 cc. An additional 200 cc. of citrated blood was given, and the baby's condition improved. Three hours later twitchings of the entire body were noted; a diagnosis of hypocalcemic tetany was made, based upon the marked blood loss and replacement by citrated blood. This condition was relieved by the intravenous administration of 9 cc. 10% calcium gluconate. The temperature was 40.1°C. 16 hr. after operation, and steadily dropped to 37.4°C. during the next 12 hr. Urinary

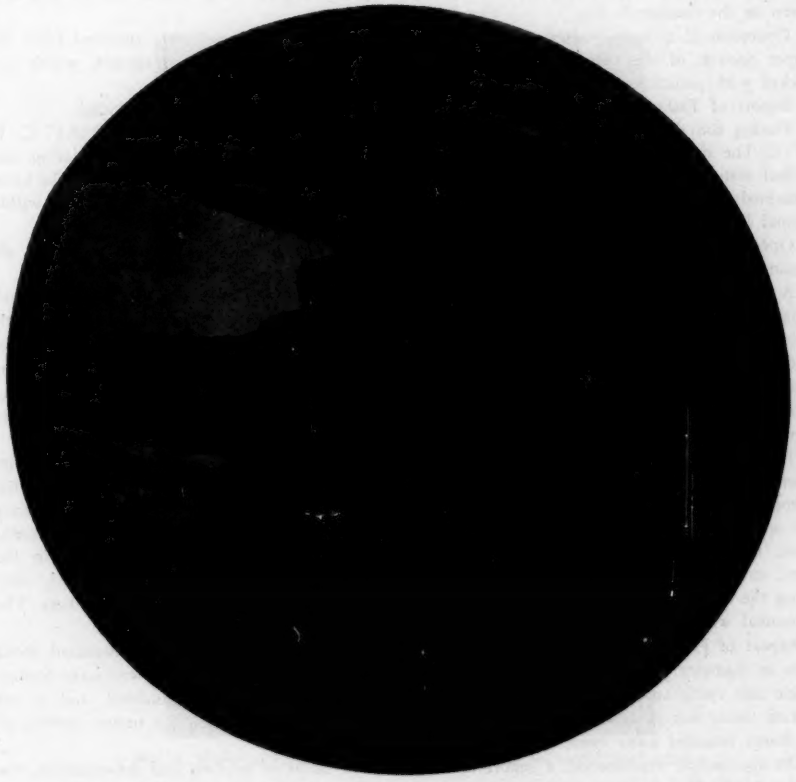


FIG. 3. Microscopic section of tumor showing cartilage, bone, and cystic area lined by ciliated epithelium (X30).

retention was relieved by an indwelling urethral catheter. A Levin tube was inserted into the stomach. Penicillin, 100,000 units daily by intramuscular injection, was started.

The infant's condition improved during the remainder of the first postoperative week. The highest daily temperatures varied from 37.7°C. to 39.2°C. There was occasional vomiting, but most feedings were retained. The urinary output through the indwelling catheter seemed adequate, and the stools were normal in number and appearance. Urine contained many WBC, singly and in clumps; culture yielded B. coli. The packing was removed from the pelvic cavity on the third day. A transfusion of 60 cc. packed red cells was given on the sixth day because RBC was 2.97 million/cmm. and Hgb. 8 gm./100 cc. Sternal marrow examination on the seventh day revealed no tumor cells.

During the second postoperative week the highest daily temperature varied from 38.4° C.

to 40.3° C. There was a brown, serous discharge from the wound, which showed little healing, and the presence of a necrotic presacral mass. The indwelling urethral catheter was removed, and streptomycin, 0.24 gm. daily by intramuscular injection, was started on the eighth day. There was a reduction in the number of WBC in the urine, but the culture was B. coli. Penicillin, a total of 1,824,000 units, and streptomycin, a total of 0.72 gm., were discontinued on the tenth day. Sulfadiazine, 0.78 gm. daily, was started. There was slight vomiting, and the stools were more frequent and loose. Weight was 4,535 gm. Three WBC during the second week showed leukocytosis; the highest Hgb. was 11 gm./100 cc. A transfusion of 60 cc. packed red blood cells was given on the fourteenth day.

Operation II (15 days after operation I): Masses of necrotic tissue were removed from the upper portion of the pelvic cavity, leaving a large cavity, anterior to the sacrum, which was packed with penicillin gauze.

Report of Pathology: Necrotic tissue with inflammatory exudate; no tumor found.

During the third postoperative week the highest daily temperature varied from 38.4° C. to 40° C. The abdominal mass felt a little smaller. The large pelvic cavity was clean, granulating, and packed with penicillin gauze. Daily slight vomiting stopped at the end of the third week. The urine contained few WBC. RBC was 3.9 million/cmm. and Hgb. 12.5 gm./100 cc. WBC was within normal limits.

Operation III (24 days after operation I): Under ether anesthesia a transverse, lower abdominal incision was made, dividing both rectus and oblique musculatures.

A large tumor presented, filling most of the lower abdomen. The neoplasm was retroperitoneal, spherical in outline, and measured about 8 cm. in diameter; it was pink-to-gray in color, partly solid and partly cystic with thick walls. Hard nodules were felt within the tumor. The distended urinary bladder overlaid a portion of the anterior and lateral surfaces of the tumor. The uterus, Fallopian tubes, and ovaries were adherent to the posterior surface of the bladder, and covered a part of the anterior surface of the tumor. Loops of small intestine and the cecum were normal in appearance. The sigmoid colon was compressed and displaced by the tumor.

The loops of small intestine were displaced from the operative field. The posterior peritoneum covering the tumor was incised, and a plane of cleavage was established. Mobilization of the tumor was made difficult by fixation of its lower portion in the pelvis, where it was necrotic and adherent to the sacrum. After removal of the neoplasm, the lower lumbar retroperitoneal space, the pelvic cavity, and the lower ends of both ureters were exposed. Bleeding in the pelvic cavity was controlled. The layers of the posterior peritoneum were approximated, after filling the retroperitoneal area and pelvis with about 15,000 units of penicillin in solution. The abdominal wall was then closed.

Report of Pathology: The specimen was a partially encapsulated tumor which measured about 8 cm. in diameter. The capsular surface was smooth, pink-to-grey in color, and showed many hemorrhagic and cystic subcapsular areas. One edge of the tumor was not encapsulated, and a soft pinkish tissue was present. Several small hard masses were palpable within the tumor. Section of the tumor revealed many cystic areas and necrotic tissue.

On microscopic examination, a report of teratoma with areas of necrosis and inflammation was made; mitotic figures were noted.

Course: An intravenous infusion of 5% dextrose in saline and 200 cc. citrated blood were given during the operation. After operation, the infant was placed in an oxygen cubicle. An indwelling catheter was inserted into the bladder. Penicillin, 160,000 units daily by intramuscular injection, was started.

The infant reacted well to operation, and her condition remained good throughout the rest of the period of hospitalization. The administration of oxygen and intravenous fluids were stopped on the second postoperative day. The indwelling catheter was removed on the fourth day. Penicillin was discontinued on the fifth day, a total of 800,000 units. The febrile preoperative course quickly changed, and the temperature remained normal after the fourth postoperative day. The appetite was good, and there was no vomiting. The abdominal wound healed by primary union, and the skin sutures were removed on the eighth day. The urinary output was adequate, and the urines contained rare WBC. The large space in the pelvic cavity progressively closed with the aid of penicillin gauze packings. Infant was discharged 53 days after third operation, weighing 5.9 kg.

Follow-up examination revealed that the child progressed well and steadily gained weight. She was readmitted to the Mount Sinai Hospital, at the age of 1 yr., because of intermittent fever and pyuria for 3 mo. During this period, treatment with sulfadiazine and penicillin was not effective. Physical examination revealed no abnormalities. The wounds were firmly healed. The weight was 10 kg. During observation for 5 days the highest temperature was 38.1° C. Urinalyses revealed rare WBC on microscopic examination, and B. coli and enterococcus on culture. Intravenous pyelography showed some dilatation of the renal pelves and calyces and the ureters; the bladder appeared normal. Streptomycin, 0.5 gm. daily, was given for 5 days, a total of 2.5 gm. Following

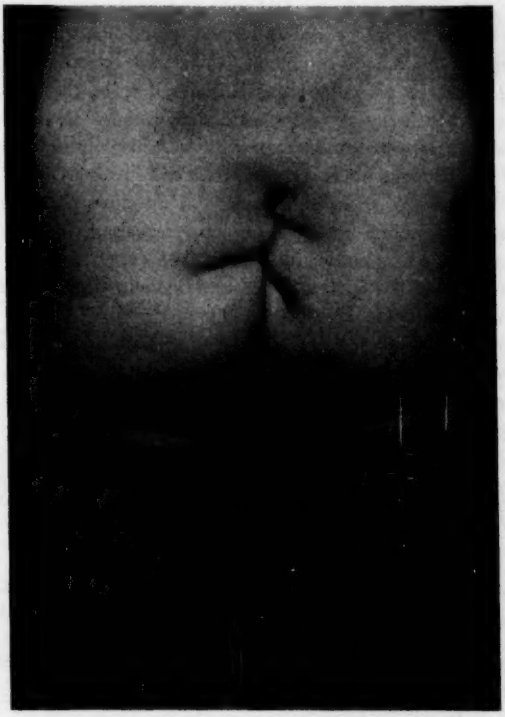


FIG. 4. View of back at 3 yr. of age, showing sacrococcygeal scar.

therapy, the temperature remained below 37.5° C.; urinalysis was normal on microscopic examination and sterile on culture. The child was discharged.

Some serosanguinous drainage from the sacral wound was noted when the infant was 16 mo. old, and the child was readmitted to the hospital. Physical examination revealed a small sinus in the sacral wound. There were no other abnormalities. RGs of the chest, long bones, skull and spine showed no abnormalities. The sacral sinus was explored and found to lead into a cavity, about 3 cm. in diameter, between the skin and the posterior surface of the sacrum. The cavity was filled with soft granulation tissue which was removed with the curette. The walls of the cavity appeared normal, and there was no gross evidence of tumor tissue. The cavity was packed. The report of pathology was fragments of inflamed granulation tissue with foreign body giant cell reaction; no evidence of tumor. The child was discharged, and the sinus and cavity were healed 5 wk. after discharge.

Follow-up examination, at the age of 3 yr., revealed normal mental and physical development; the

weight was 13.8 kg., and the height was 91 cm. The abdomen was of normal contour presenting a firmly healed wound in its lower portion. The sacral wound was solidly healed (Fig. 4). Satisfactory progress has continued to date—4 4/12 yr. after operation.

Comment: Although much of the tumor was composed of mature tissues, the pathologist classified the tumor as malignant because of the presence of mitotic figures. This, combined with removal of the tumor in stages, at first caused considerable doubt as to likelihood of permanent cure.

Summary

The pathologic and clinical features, diagnosis and treatment of combined pelvic and retroperitoneal teratomas in infancy and childhood, based upon a study of 15 cases, are reviewed. One case of malignant combined pelvic and retroperitoneal teratoma with recovery for 4 4/12 years is presented; this is believed to be the first reported cure of this condition.

Combined pelvic and retroperitoneal teratomas were usually noted in female infants under the age of 1 year as large tumors in the pelvis and lower abdomen, with or without extension into the buttocks, often causing urinary or intestinal obstruction, readily diagnosed by rectal and abdominal examination, and revealing areas of calcification or ossification on roentgenologic examination.

In this group of 15, 4 of the teratomas had undergone malignant changes, and 4 had not been operated upon and were described at autopsy.

Successful treatment of combined pelvic and retroperitoneal teratomas was dependent upon early operation, careful operative technic through staged posterior and abdominal incisions, and adequate preoperative and postoperative management. The operative mortality was 20%.

A long term recovery rate of 15% in combined pelvic and retroperitoneal teratomas is in marked contrast to the reported cures with sacrococcygeal teratomas (68%) and retroperitoneal teratomas (42%).

References

1. Chaffin, L., Clinical aspects of sacrococcygeal teratomas, Surg., Gynec. & Obst. **69**:337, 1939.
2. Ravitch, M. M., and Smith, E. I., Sacrococcygeal teratoma in infants and children, Surgery **30**:733, 1951.
3. Gross, R. E., Clatworthy, H. W., and Meeker, I. A., Sacrococcygeal teratomas in infants and children, Surg., Gynec. & Obst. **92**:341, 1951.
4. Arnheim, E. E., Retroperitoneal termatomas in infancy and childhood, Pediatrics **8**:309, 1951.
5. Brown, R. K., and Brown, E. C., Sacrococcygeal teratoma with urinary retention, Arch. Surg. **60**:535, 1950.
6. Brown, R. K., Personal communication to the author.
7. Lisco, H., Malignant tumors developing in sacrococcygeal teratomata, Ann. Surg. **115**:378, 1942.
8. Meister, W., Kritische Betrachtungen zur Entstehung der angeboren Steißgewachse unter Zugrundelegung zweier beobachteter Falle, Arch. f. path. Anat. **288**:286, 1933.
9. Rhoden, A. E., Precocious sexual and somatic development in male infant with presacral teratoma containing androgen-producing tissue, J. Clin. Endocrinol. **4**:185, 1944.
10. Riker, W., and Potts, W. J., Sacrococcygeal teratomata in infancy, Ann. Surg. **128**:89, 1948.
11. Sawday, A. E., Partial intestinal obstruction in child due to postrectal teratoma, Brit. M. J. **2**:685, 1925.
12. Seggers, W., Beitrage zur Frage der Steißtertatome, Beitr. z. path. Anat. u. z. allg. Path. **93**:491, 1934.
13. Woodruff, S. R., and Begner, J. A., Sacroccygeal teratoma in infant of five months causing acute urinary obstruction, J. Urol. **54**:177, 1945.
14. Wright, C. B., Sacrococcygeal teratomas, Am. Surgeon **17**:196, 1951.

15. Willis, R. A., Pathology of Tumors, London, Butterworth & Co., Ltd. 1948, p. 940.
16. Ingraham, F. D., Spina Bifida and Cranium Bifidum, Cambridge, Harvard University Press, 1944, p. 6.
17. Alexander, C. M., and Stevenson, L. D., Sacral spina bifida, intrapelvic meningocele, and sacrococcygeal teratoma, Am. J. Clin. Path. **16**:466, 1946.
18. Montgomery, A. H., and Wolman, I. J., Sacrococcygeal chordomas in children, Am. J. Dis. Child. **46**:1263, 1933.

SPANISH ABSTRACT

Teratomas en la Infancia de Localización Pélvica y Retroperitoneal Combinada

Aunque el sitio mas común de los teratomas de la infancia es la región sacrococcígea y se encuentran reportados 466 casos en la literatura, y le sigue en importancia la localización en el espacio retroperitoneal con 41 casos registrados, la localización combinada presacra y retroperitoneal no es rara y este estudio presenta las características clínicas, patológicas, diagnósticas y terapeúticas de 15 casos de teratomas pélvico y retroperitoneal combinados, de los cuales uno de ellos, cuyo caracter maligno se comprobó histológicamente por la presencia de mitosis, aunque la mayor parte de los tejidos eran maduros, ha continuado clínicamente sano hasta 4 años 4 meses después de operado y se cree que sea el primer caso curado que se ha reportado en la literatura.

Se trató de una niña de 2 meses de edad con un tumor en la región glútea que estaba presente desde el nacimiento. A los 2 meses ocupaba la mitad inferior del abdomen pared lateral derecha y posterior de la pelvis, y hacía prominencia en la región sacrococcígea extendiéndose a ambas regiones glúteas a través del pliegue interglúteo. Radiológicamente se visualizaron algunas áreas irregulares de calcificaciónes intratumorales pero no había metástasis ni en pulmones ni en huesos.

En una primera intervención quirúrgica se extirpó gran parte de la tumoración glútea y pélvica resecando coccis y segmento inferior de sacro seguida de una segunda usando igual vía para completar la extirpación de restos de tejido tumoral necrótico de la parte superior de la cavidad pélvica, y finalmente en un tercer tiempo quirúrgico se extrajo la porción tumoral retroperitoneal situada en el abdomen a través de una incisión abdominal inferior.

Las características patológicas de los teratomas pélvicos y retroperitoneales combinados son las de ungran tumor quístico y sólido que nace en la región presacra y se extiende hacia arriba en el abdomen a través del espacio retroperitoneal aunque en algunos casos su crecimiento se hace hacia abajo y atras haciendo prominencia en una o ambas regiones glúteas o hacia las extremidades inferiores. La porción pélvica del tumor está limitada anteriormente por el recto y posteriormente por el sacro y coccis comprimiendo eventualmente el recto, vejiga urinaria y ureteros. Casi siempre están pegados al coccis y sacro. Contienen elementos embrionarios ecto, endo y mesodermicos; los mas benignos estan formados por tejidos completamente maduros sin signos de proliferación; los mas malignos tienen abundante tejido embrionario inmaduro. La incidencia de malignidad en esta serie fué de 38% en contraste con la de los teratomas sacrococcígeos que varían de 9 a 27.5% y de los retroperitoneales de 6.8%.

Las manifestaciones clínicas variaron con la localización anatómica del tumor; en 10 casos había crecimiento en la región sacrococcígea, en 5 en la pelvis y abdomen inferior exclusivamente, en ambos grupos el examen rectal y abdominal descubrió el tumor. La sintomatología fué de compresión vesical, ureteral, o rectal en 10 casos produciendo obstrucción intestinal o urinaria. Fueron frecuentes las calcificaciones intratumorales y en un enfermo se encontró hueso bien conformado en las radiografías simples. En vista de la frecuencia de metastásis en pulmones en los casos malignos no debe olvidarse tomar radiografías de estos.

El diagnóstico diferencial debe hacerse con el mielomeningocele de la región presacra, de la región lumbar que es su sitio habitual, los cordomas sacrococcígeos que por las lesiones destructivas del sacro son fáciles de eliminar excepto de aquellos teratomas con degeneración maligna, y finalmente con ependimomas de la cola de caballo y neuroblastoma de localización pélvica y retroperitoneal.

El tratamiento de elección es la extirpación quirúrgica temprana y completa.

106 East 78th Street

GLYCOGEN DISEASE OF THE HEART

Report of Two Cases Occurring in Siblings

By ALFRED W. CHILDS, M.D., ROBERT F. CROSE, M.D., AND PATRICIA H. HENDERSON, M.D.
San Francisco

THE clinical picture of glycogen disease of the heart has frequently been confused with other clinical entities, including hypothyroidism,[1-4] mongolism,[1] and amyotonia congenita.[1,5-7]

Two infants have been observed in the same family who died of this disease, and in whom the correct diagnosis was considered in the first and anticipated in the second —and, in both, proved by postmortem examination. These two cases show close correlation of clinical and pathologic findings. The clinical picture was characterized by progressive weakness, areflexia, and susceptibility to secondary infections. There was also progressive hepatomegaly and cardiomegaly. The pathologic findings were characterized by marked glycogen storage in skeletal, cardiac and smooth muscle, liver and nerve cells of the central and autonomic nervous systems. In addition, many other tissues showed some glycogen storage. The storage in the skeletal muscle was so marked as to result in degeneration of the muscle fibers.

In presenting these cases the authors hope to further clarify the clinical picture of glycogen disease of the heart.

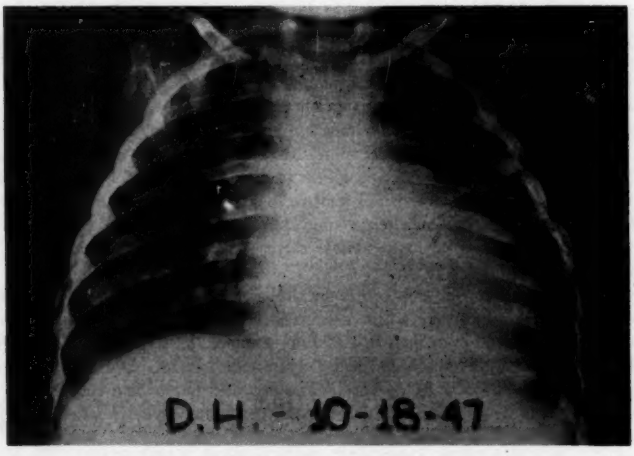


FIG. 1. Case 1. Chest RG at 11 mo. Cardiac enlargement.

CASE REPORTS

Case 1: D. H., an 11 mo. old male, was first seen in the hospital because of generalized and progressive weakness and failure to gain weight. He had weak atonic musculature, areflexia, and

From the Divisions of Pediatrics and Pathology, University of California School of Medicine, San Francisco.

(Received for publication July 10, 1951.)

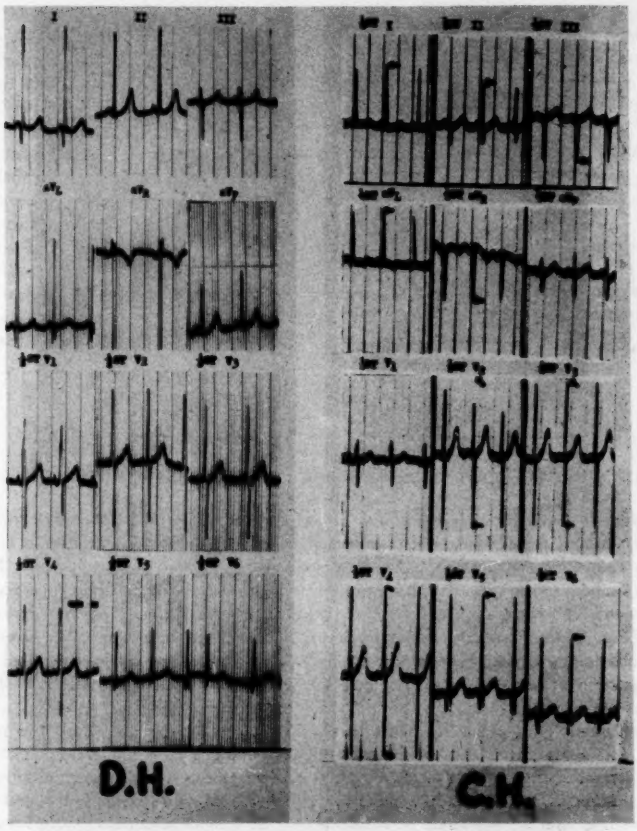


FIG. 2. ECG of Case 1* (left) and Case 2† (right). High voltage.

* ⅓ Standardization deflection (1 mv. equals 3⅓ mm.)
† ½ Standardization deflection (1 mv. equals 5 mm.)

both cardiac and hepatic enlargement. Discharge diagnosis was congenital heart disease of undetermined type. Three months later he re-entered with cough and fever. Weakness and cardiohepatomegaly were present as before and coarse rales were heard throughout both lung fields. Course was stormy and despite therapy, he died 4 days after entry.

Chest RGs (Fig. 1) showed marked cardiac enlargement in both transverse and A-P diameters. Esophagus was deviated to R, and posteriorly in midportion. Lung fields were clear, without evidence of vascular engorgement. Impression was congenital heart disease with marked cardiac enlargement, predominantly L sided.

Electrocardiography (Fig. 2) rate 90/min.; P-R 0.11 sec.; QRS 0.08 sec.; axis of +20; intermediate heart. Huge QRS voltage was noted, R1 = 30 mm. and with ⅓ standardization, RV5 = 16 mm. Conclusion was that high voltage probably indicated L ventricular hypertrophy.

Case 2: C. H., sister of previous patient was born at the University of California Hospital 2 mo. after her sibling (D. H.) died and was considered normal. Chest RGs, oral glucose tolerance curve, complete blood count and urinalysis were within normal limits. Early growth and development was satisfactory, but at 8 mo. of age she developed a viral pneumonia. She became icteric and the condition persisted for 2 mo. From this time on, progressive weakness and lethargy were

FIG. 3. Case 2. Chest RG at 16 mo. Cardiac enlargement.

noted, leading to hospitalization at 16 mo. of age for study. She had extremely weak and atonic muscles; was areflexic; and could not pull herself up or stand. Electrocardiograph (Fig. 2): sinus tachycardia 136/min.; P-R 0.07 sec.; QRS 0.06 sec.; axis −10; semihorizontal heart. T-waves were diphasic in leads 1 and a VL, and QRS voltage was high. Conclusion was abnormal record, T-wave abnormality and high voltage probably due to L ventricular hypertrophy. Chest RG showed cardiac enlargement (Fig. 3). Cardiomegaly and hepatomegaly were present. Glucose tolerance curves were again within normal limits. During hospitalization she developed atelectasis and had repeated fecal impactions. Progression of weakness was such that she was unable to hold up her head shortly before death on the 44th day.

Levels of blood glucose for tolerance tests (chart 1) were determined by the microtitration method of Miller-van Slyke and are in mg./100 cc. In the authors' laboratory, 120 to 130 are considered normal fasting glucose levels. Oral test dose of glucose was 15 gm.; the intravenous dose was 5 gm. Insulin, ¼ unit/kg. body weight, was given 10 min. after glucose in one oral glucose test. Adrenalin without glucose was given in a dose of 0.03 cc. 1:1000 solution/kg. body weight to determine response of blood glucose to adrenalin.

PATHOLOGIC REPORT

Case 1 (U.A. 4824). Autopsy was performed 4 hr. after death.

Gross Description: Heart enlarged and weighed 138 gm. (normal 45 gm.[8]), of globular

CHART 1. CASE 2, TOLERANCE TESTS

Time	5 Days of Age	16 mo. of Age					
Type of Tolerance Test	Oral Glucose	Oral Glucose #1	Oral Glucose #2	Intravenous Glucose		Oral Glucose with Insulin	Adrenalin
				Blood Sugar	Urine		
Fasting	148	155	132	118	Blue	126	126
10 min.				300	Orange		
30 min.	260	156	135	252	Brown	171	148
60 min.	202	200	185	186	Orange	152	174
90 min.				138	Blue Green		
120 min.	178	184	157	118	Blue	112	154
180 min.	152	158	150			98	128

configuration and measured 6 by 8 by 10 cm. Right ventricle measured 0.4 cm. in thickness, L ventricle 1.2 cm. and interventricular septum 1.4 cm. Muscle was firm and had a pale greyish pink color. Endocardium, valves, coronary vessels and great vessels had a normal appearance.

Lungs were moderately congested and had areas of atelectasis.

Liver was enlarged, weighed 480 gm. (normal 304 gm.), and had a normal configuration and capsule. Color was mottled pinkish yellow, and lobules appeared swollen.

Ureters were moderately and uniformly dilated. Remainder of urogenital system was normal.

Gastrointestinal system, spleen, bone marrow, and endocrine glands appeared normal.

Skeletal musculature was underdeveloped in appearance and had a pale pink color.

Brain was pale, but otherwise normal.

Microscopic Description: Tissues were fixed in dilute solution of formaldehyde and in Zenker's fluid, and were imbedded in paraffin. Sections were stained with hematoxylin and eosin. Glycogen was demonstrated with Fuelgen-Bauer stain[9] and was lost after incubation of sections with saliva.

Cardiac muscle fibers were altered by fusiform, indistinctly outlined, perinuclear clear spaces which contained fibrillar and granular eosinophilic material. The myofibrils were fragmented and dis-

FIG. 4. Case 2. Left ventricular wall stained by Fuelgen-Bauer method and showing (from left to right) myocardium, subendocardial Purkinje fibers, and endocardium which contains layer of smooth muscle. Note abundant stained material in both smooth muscle and cardiac muscle; x 100.

placed to the peripherae of the fibers. Muscle fiber diameters appeared increased. Fiber sheaths were intact. Nuclei, which appeared normal, rested transversely within the vacuolar areas. Glycogen stain showed extensive deposition in the sarcoplasm, more marked in fibers near the valve rings and in Purkinje fibers (Fig. 4).

Some of the surface epicardial cells were cuboidal and contained glycogen. There was a small amount of glycogen in many of the connective tissue cells of the endocardium and valves, and a large amount in the subendocardial smooth muscles. Endocardial structures were otherwise normal.

All smooth muscle cells in the various tissues were altered by central, fusiform, clear vacuoles of variable size. The sarcoplasm was compressed to the peripherae; and the nuclei, which appeared normal, rested in the centers of the vacuoles. This change gave the smooth muscle a pale lacy appearance. After glycogen stain the blood vessels and the smooth muscle coats of the viscera stood out as purple-red rings or sheets (Fig. 4 and Fig. 5).

Lungs showed scattered areas of atelectasis and congestion of the vessels. Some of the cells of the alveolar walls had clear vacuoles.

Liver cells were swollen with multiple small indistinct vacuoles, which were filled with glycogen. These cells compressed the sinusoids. The nuclei, which appeared normal, were eccentrically situ-

FIG. 5. Case 1. Small meningeal vessel shows clear vacuolation without degenerative changes in smooth muscle cells; hematoxylin and eosin; x 450.

ated. A small number of fat droplets were shown with Sudan IV stain. The distribution of glycogen was irregular.

Pancreatic islets appeared normal. There were numerous small basal vacuoles in the acinar cells.

Glomerular cells of the kidneys often were vacuolated and contained a moderate amount of glycogen. Cytoplasm of the epithelial cells of the distal convolution, parts of the loop of Henle, and the renal pelvis and bladder had a foamy appearance and contained a moderate amount of glycogen.

Glycogen was seen in cardiovascular endothelial cells, histiocytes, and reticuloendothelial cells, although these cells appeared normal in sections stained with hematoxylin and eosin.

Adrenal glands had increased vacuolation of the cells of the zona glomerulosa, similar to that seen in Case 2. Pituitary and thyroid glands appeared normal.

Thymus gland had a loose structure with a reduced number of lymphocytes in the cortical areas and numerous Hassal's bodies.

Lymph nodes and bone marrow were hyperplastic.

Sections of various skeletal muscles were taken from tissue fixed in Zenker's fluid. All fibers showed a similar extensive fragmentation or loss of myofibrillary structure within an intact sarcolemma framework, and contained a large amount of glycogen. Many fibers contained granular or fibrillar matter which sometimes stained with eosin, sometimes was basophilic. The nuclei were normal or slightly shrunken.

Many of the nerve cells of the autonomic and central nervous systems were swollen with glycogen and had convex borders. Nissl bodies were seen at the borders of the cells (Fig. 6). These changes were most marked in the motor cells of the brain stem and spinal cord; little or no change was found in the cerebral and cerebellar cortices, the thalamus, and the corpus striatum.

Summary of Pathologic Findings: 1. Glycogen storage disease with major deposition in skeletal and cardiac muscle, and minor deposition in liver, nerve cells and smooth muscle. 2. Partial pulmonary atelectasis.

Case 2, C. H. (U.A. 49131). Autopsy was performed 2 hr. after death.

Gross Description: Heart weighed 154 gm. (normal 48 gm.) and measured 7.5 cm. from the

FIG. 6. Case 2. Section of medulla showing 2 nerve cells distended with small clear vacuoles. Note nuclei and Nissl's bodies near processes; hematoxylin and eosin; x 450.

root of the aorta to the apex along the anterior septal border. Right ventricular wall averaged 0.4 cm. in thickness and L ventricle 2.0 cm. Heart muscle was firm and was pale bluish pink in color, reminiscent of salmon flesh. A thrombus 1 cm. in diameter was attached to the endocardium at the apex of L ventricle. Valves, coronary vessels and great vessels appeared normal.

Lungs had mosaic patches of atelectasis and lower lobes adhered to the mediastinum.

Liver weighed 600 gm. (normal 1331 gm.) and had a normal configuration, capsule, and consistency. Color was mottled.

Kidneys contained several infarcts, but were otherwise normal in appearance.

Skeletal muscle had an unusual pale bluish pink color similar to that of the heart.

Gastrointestinal system, genitourinary tract, spleen, bone marrow and endocrine glands were grossly normal.

Brain was pale. Sagittal sinus and adjacent cerebral vessels contained thrombi.

Microscopic Description: Tissues were fixed in dilute solution of formaldehyde and embedded in paraffin. Stains were the same as Case 1.

Microscopic appearance of the heart was similar to that described in Case 1 (Fig. 4). Mural thrombus showed little organization.

Smooth muscle showed a vacuolar appearance and glycogen deposition similar to Case 1 (Fig. 5).

Lungs had scattered areas of atelectasis and small patches of bronchopneumonia.

Liver cells were distended with glycogen and appeared similar to Case 1. Density of glycogen was greater in the central parts of the lobules.

A small amount of glycogen was seen in both acinar and islet cells of pancreas.

A small amount of glycogen was seen in the cardiovascular endothelial cells, reticuloendothelial cells, cells of the pulmonary alveolar walls, and histiocytes. When stained with hematoxylin and eosin, these cells appeared normal or had small indistinct vacuoles.

Appearance and distribution of glycogen in kidneys were similar to Case 1. Infarcts of kidneys appeared to be recent. Epithelium of the renal pelvis and bladder had a structure and glycogen deposition similar to Case 1.

Thymus gland had a reduced amount of lymphoid tissue and numerous Hassal's bodies.

Zona glomerulosa of adrenal glands was sharply defined and cells of this layer were pale and vacuolated. Cells of the inner zones were filled with glycogen; there was a much smaller amount in the zona glomerulosa. There was a small amount of glycogen in the medullary cells.

Ovaries and genital tract were normal except for the smooth muscle change described. Pituitary and thyroid glands were normal. Bone marrow and lymph nodes were hyperplastic.

Skeletal muscles showed extensive degeneration and glycogen deposition similar to that in Case 1 (Fig. 7). Basophilic granular and fibrillar material was less frequent than in Case 1, possibly because of difference in fixatives.

There was glycogen deposition in nerve cells similar to that in Case 1. This was most pronounced in the motor cells of the brain stem and spinal cord (Fig. 6). Vacuolar change was seen in most of the nerve cells of midbrain, rectum, dentate nucleus of the cerebellum, pons, medulla and spinal cord. Glycogen was noted also in some of the glial cells and in the ependymal cells.

Summary of Pathologic Findings: 1. Glycogen storage disease with major deposits in skeletal and cardiac musculature and minor deposits in liver, nerve cells and smooth muscle. 2. Mural thrombus

FIG. 7. Case 1. Psoas muscle showing extensive degeneration. Note remaining fragments of myofibril bundles and granular debris in vacuolar spaces; hematoxylin and eosin; x 450.

of left ventricle. 3. Partial pulmonary atelectasis and terminal bronchopneumonia. 4. Infarct of both kidneys.

DISCUSSION

The family history in these patients may be of some significance, in that a maternal first cousin in the second year of life had what appeared to be true amyotonia congenita. Glycogen storage disease in these patients was a progressive disabling disease. Examinations showed progressive enlargement of heart and liver. Autopsy disclosed marked deposition of glycogen in heart, skeletal and smooth muscles; liver; and nerve cells. Similar extensive involvement has been reported in other cases and was summarized recently by di Sant'Agnese et al.[10] The amount of glycogen found in a given tissue appears to be proportional to the relative role that substance plays in the metabolic activity of that tissue.

In the two cases reported here the hearts were more than twice normal weight. Probably a large part of this increased weight was due to storage of glycogen. In Case 2 the heart, at five days of age, appeared to be within normal limits. This indicates that al-

though the primary defect may have been present at birth, the disease was progressive because of the continuous depositions of glycogen which were not normally metabolized. Inasmuch as the blood glucose curves were normal, it is probable that ultimate death was due to organ impairment by excess glycogen rather than deficiency of available blood glucose suitable for tissue oxidation.

Electrocardiographic findings have demonstrated no clearcut diagnostic criteria as yet. The only common finding noted in those cases where the cardiogram was reported[1,3,10–13] has been sinus tachycardia. The cases of Clement[1] and these two cases show unusually high voltages in the QRS complex. Evidence of myocardial damage[1,11] and conduction disruption[10] have been reported but the cardiograms in those cases were taken late in the clinical course and may represent terminal changes.

While the hearts in these cases were more than twice normal weight, presumably due to excess glycogen, there was no apparent enlargement or pseudo-hypertrophy of the skeletal muscle. Macroglossia, which was noted in the cases of Clement,[1] Hertz,[2] Sprague,[3] Schneider,[4] and Wolff[5] was not present in the cases reported here. The only gross abnormalities of the skeletal muscle were flabbiness and a peculiar pale gray-pink color. These findings are similar to those in other reported cases of this type of glycogen disease. Apparently the glycogen storage in voluntary muscle results in muscle degeneration sufficient to avoid any increase in size. The microscopic changes are indicative of extensive degeneration. Lack of enlargement of this muscle might also result from disuse atrophy secondary to the combined neuro-muscular lesion.

The present authors' cases showed glycogen storage in the nerve cells of the brain stem and spinal cord. The major neural involvement was in the motor cells. It is difficult to determine the relative importance of the neural and muscular changes in causing the clinical picture of progressive muscular weakness. Either lesion seen alone could be accepted as a cause for this part of the clinical picture.

The appearance of the smooth muscle in these cases was not as suggestive of functional derangement as was the striking disruption of the striated muscle. However, the persistent fecal impaction and the accumulation of secretions in the bronchial tree may have been manifestations of smooth muscle weakness. The functional effect of the glycogen storage in the autonomic nerve cells cannot be easily delineated.

Glycogen was demonstrated in small amounts in the reticuloendothelial cells of these children. Perhaps the glycogen in this tissue may have resulted partially or completely from phagocytosis of material liberated from degenerating muscle.

Glycogen storage disease must be strongly considered where progressive hepatomegaly, with or without disordered carbohydrate metabolism; cardiomegaly without significant murmurs; and severe muscular weakness are found associated. Differentiation from hypothyroidism, mongolism, and amyotonia congenita can probably be made by careful examination and the usual laboratory methods. Muscle biopsy may be of confirmatory value.

Summary

Two cases of siblings with glycogen storage disease of the heart are reported. The clinical picture was characterized by progressive weakness, areflexia, and susceptibility to secondary infections. There was also progressive hepatomegaly and cardiomegaly.

The pathologic findings correlated well with the clinical and were characterized by marked glycogen storage in skeletal, heart, and smooth muscle, the liver, and nerve cells of the central and autonomic nervous systems. In addition, many other tissues

showed some glycogen storage. Storage in the skeletal muscle was so marked as to result in degeneration of the muscle fibers.

The familial aspect of this disease is again noted. Suggestions regarding differential diagnosis are made.

ACKNOWLEDGMENT

The authors wish to express their appreciation to Alex Contopolous, M.D., Department of Pharmacology of the University of California School of Medicine, and to William C. Deamer, M.D., and Henry K. Silver, M.D., for their advice and assistance.

REFERENCES

1. Clement, D. H., and Godman, G. C., Glycogen disease resembling mongolism, cretinism and amyotonia congenita, J. Pediat. **36**:11, 1950.
2. Hertz, W., and Jeckeln, E., Glykogenspeicherkrankheit unter dem klinischen Bilde des Myxodems, Ztschr. f. Kinderh. **58**:247, 1936.
3. Sprague, H., Bland, E., and White, P. D., Congenital idiopathic hypertrophy of heart: Case with unusual family history, Am. J. Dis. Child. **41**:877, 1931.
4. Schneider, J., Infantile Herzhypertrophie. Beitrag zur Frage der Glykogenspeicherungskrankheit, Helvet. paediat. acta **1**:368, 1945.
5. Wolff, K., Beitrag zur Morphologie und Chemie der Glykogenspeicherkrankheit, Beitr. z. path. Anat. **97**:289, 1936.
6. Gunther, R., Beitrag zur Kenntnis der Glykogen-Speicherkrankheit, Virchows Arch. f. path. Anat. **304**:87, 1939.
7. Humphreys, E., and Kato, K., Glycogen storage disease, Am. J. Path. **10**:589, 1934.
8. Coppoletta, J. M., and Wolbach, S. B., Body length and organ weights of infants, Am. J. Path. **9**:55, 1933.
9. Bensley, R. R., and Bensley, S. H., Hand Book of Histological and Cytological Technique, Chicago, University of Chicago Press, 1938, p. 105.
10. di Sant'Agnese, P. A. Andersen, Dorothy H., Mason, H. H., and Bauman, W. A., Glycogen storage disease of heart. II. Critical review of literature, PEDIATRICS **6**:607, 1950.
11. Antopol, W., Boas, E. P., Levison, W., and Tuchman, L., Cardiac hypertrophy caused by glycogen storage disease in 15 year old boy, Am. Heart J. **20**:546, 1940.
12. Mutgeert, B. L., Over aangeboren groot Hart, Speciall in verband met de Glycogeenzieket, Maandschr. v. kindergeneesk. **6**:233, 1936.
13. di Sant'Agnese, P. A., Andersen, Dorothy H., Mason, H. H., and Bauman, W. A., Glycogen storage disease of heart. I. Report of 2 cases in siblings with chemical and pathological studies, PEDIATRICS **6**:402, 1950.

SPANISH ABSTRACT

Enfermedad Glicogénica del Corazón: Relato de Dos Casos en Hermanos

Los autores presentan dos casos de enfermedad glicogénica del corazón en dos hermanos. El cuadro clínico se caracterizó por debilidad progresiva, arreflexia, susceptibilidad a las infecciones secundarias y desarrollo progresivo de hepato y cardiomegalia.

El primer caso fué un niño de 11 meses de edad, que fué llevado al médico por debilidad progresiva, y falta de aumento de peso. Se trataba de un niño con musculatura débil, atónica, con arreflexia y cardio y hepatomegalia, haciéndose el diagnóstico de enfermedad congénita del corazón de tipo indeterminado. Tres meses mas tarde comenzó con tos y fiebre y estertores gruesos en ambos campos pulmonares. Su evolución fué severa y murió a los 7 días de iniciado el cuadro febril.

El segundo caso fué el de la hermana del anterior que al nacimiento se le encontró completamente normal pues las radiografías de tórax, curvas de tolerancia a la glucosa por vía oral, biometrías hemáticas y análisis de orina fueron negativos. Hasta los 8 meses de edad su crecimiento

y desarrollo fueron satisfactorios. A esa edad contrajo una neumonía a virus y se puso ictérica permaneciendo así por 2 meses. Desde ese momento se apreció debilidad progresiva y letargia y a los 18 meses su estado de debilidad y atonía muscular eran extremos, no tenía reflejos, y no había motilidad espontánea de las extremidades e imposibilidad para quedarse de pie. Existía cardiomegalia y hepatomegalia. Las curvas de tolerancia a la glucosa fueron nuevamente normales. Posteriormente presentó atelectasia pulmonar, constipación severa con escíbalas y su debilidad progresó a tal grado que era incapaz de sostener su cabeza poco antes de que muriera, a los 17½ meses de edad.

La autopsia de ambos casos demostró depósitos abundantes de glicógeno en el corazón, huesos, músculos lisos y estriados, hígado y células nerviosas; en menores cantidades en las células reticuloendoteliales, pancreas suprarrenales, endotelio vascular, endocardio, neuroglia y en algunos tejidos epiteliales. El contenido anormal de glicógeno parecía ser proporcional al papel relativo que este juega en la actividad metabólica de los tejidos afectados.

Los corazones de los enfermos pesaban más del doble de su peso normal, en gran parte por la acumulación de glicógeno, y ésta fué la que provocó la muerte probablemente por interferencia funcional, más bien que la falta de glucósa sanguínea disponible, cuando menos en el segundo caso, ya que las curvas de tolerancia de la glucosa eran normales.

En contraste, no se encontró aumento o pseudohipertrofia de los músculos del esqueleto sino que estaban flácidos y de color gris-rosa pálido. Aparentemente el almacenamiento de glicógeno en los músculos voluntarios produce degeneración en grado suficiente para evitar el aumento de tamaño o también esto puede ser por atrofia, por falta de función, secundaria a la lesión neuromuscular combinada. Efectivamente, el cuadro clínico de debilidad muscular progresiva de los enfermos pudo ser causado tanto por el almacenamiento del glicógeno en las células nerviosas del cerebro o médula espinal, mas acentuado en las células motoras, como por el exceso de glicógeno muscular.

En lo que respecta a los músculos lisos es posible que la constipación con escíblas impactadas y la acumulación de secresiones en los bronquios sean manifestaciones de debilidad de los músculos lisos.

Los autores enfatizan que debe considerarse seriamente la posibilidad de enfermedad por almacenamiento del glicógeno cuando existan asociadas hepatomegalia progresiva con o sin trastornos del metabolismo de los carbohidratos, cardiomegalia sin soplos significantes, y debilidad muscular severa, haciendose el diagnóstico diferencial con hipotiroidismo, mongolismo, y amiotonía congénita por exploración física cuidadosa, los métodos usales de laboratorio y la biopsia muscular como elemento para confirmar en definitiva el diagnóstico.

University of California Hospital

Pediatrics

VOLUME 10 AUGUST 1952 NUMBER 2

AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

PRELIMINARY PROGRAM

TWENTY-FIRST ANNUAL MEETING, PALMER HOUSE, CHICAGO

SEMINARS

(All sessions will be at the Palmer House unless otherwise noted.)

Saturday, Oct. 18 — 9:00 a.m.-12 Noon; 2-5 p.m.
Sunday, Oct. 19 — 9:00 a.m.-12 Noon; 2-5 p.m.

1. PEDIATRIC NEUROLOGY
   David Clark, M. D.
   Baltimore
2. METABOLIC DISEASES
   L. Emmett Holt, Jr., M. D.
   New York City
3. PEDIATRIC ALLERGY
   Jerome Glaser, M. D.
   Rochester, N.Y.
4. EMOTIONAL PROBLEMS IN CHILDREN
   Milton J. E. Senn, M. D.
   New Haven, Conn.
5. EMOTIONAL PROBLEMS IN CHILDREN
   Benjamin M. Spock, M. D.
   Pittsburgh
6. PEDIATRIC CARDIOLOGY
   Stanley Gibson, M. D.
   Chicago
7. VIRUS AND RICKETTSIAL DISEASES
   Horace L. Hodes, M. D.
   New York City
8. HEMATOLOGY
   Wolf W. Zuelzer, M. D.
   Detroit

* 9. ENDOCRINOLOGY
   Nathan V. Talbot, M. D.
   Boston
   Note: This seminar is for one day only, but will be given to two groups. Registrations may be made for Saturday, Oct. 18, or Sunday, Oct. 19.

*10. DISTURBANCES OF ACID BASE AND WATER METABOLISM
   Allan M. Butler, M. D.
   Boston
   Note: This seminar is for one day only, but will be given to 2 groups. Registrations may be made for Saturday, Oct. 18, or Sunday, Oct. 19.

* It is suggested that if seminar 9 is selected, seminar 10 also be selected on the following day, or vice versa.

ROUND TABLE DISCUSSIONS

Monday, Oct. 20
Tuesday, Oct. 21
9 a.m.-12 Noon

1. PSYCHOLOGICAL DISTURBANCES DURING ADOLESCENCE
   William S. Langford, M. D.
   New York City
   A. H. Vander Veer, M. D.
   Chicago
2. PEDIATRIC ENDOCRINOLOGY
   John D. Crawford, M. D.
   Boston
3. ADOLESCENT GIRL AND HER MENSTRUAL PROBLEMS
   Janet W. McArthur, M. D.
   Boston
4. CLINICAL PEDIATRIC UROLOGY
   Meridith F. Campbell, M. D.
   New York City
5. PROBLEMS OF THE PREMATURE AND NEWBORN
   Wyman C. C. Cole, M. D.
   Detroit
6. HEARING AND SPEECH DIFFICULTIES IN CHILDREN
   Harlan Bloomer, Ph. D.
   Ann Arbor, Mich.
   William G. Hardy, M. D.
   Baltimore

2-5 p.m.

7. PEDIATRIC X-RAY
   Miriam Pauls, Ph. D.
   Baltimore
   Edward B. D. Neuhauser, M. D.
   Boston
8. ACCIDENT PREVENTION IN CHILDREN
   George M. Wheatley, M. D.
   New York City
9. ENCEPHALOGRAPHY AND PNEUMOENCEPHALOGRAPHY
   Fred Gibbs, M. D.
   Chicago
10. ANTIBIOTICS
    Mark Lepper, M. D.
    Chicago
    Erwin Neter, M. D.
    Buffalo
11. MANAGEMENT OF POLIOMYELITIS INCLUDING BULBAR AND RESPIRATORY INVOLVEMENT
    A. J. Steigman, M. D.
    Louisville, Ky.
    John E. Affeldt, M. D.
    Hondo, Calif.

Tuesday, Oct. 21
Wednesday, Oct. 22
9 a.m.-12 Noon

1. USE OF A.C.T.H., CORTISONE AND ASSOCIATED SUBSTANCES
   Albert Dorfman, M. D.
   Chicago
2. RHEUMATIC FEVER
   Arild E. Hansen, M. D.
   Galveston, Texas
   Hugh McCulloch, M. D.
   Chicago
3. PROBLEMS IN CHILD PSYCHIATRY
   Leo Kanner, M. D.
   Baltimore
4. EMERGENCY CARE OF THE NEWBORN
   Edith L. Potter, M. D.
   Chicago

2-5 p.m.

5. CELIAC SYNDROME
   Dorothy H. Anderson, M. D.
   New York City
6. THE EVALUATION OF MENTAL DEFICIENCIES
   Herman Yannet, M. D.
   Southbury, Conn.
7. PEDIATRIC DERMATOLOGY
   Earl Osborne, M. D.
   Buffalo, N.Y.
8. PEDIATRIC ALLERGY
   James C. Overall, M. D.
   Nashville, Tenn.
9. BLOOD DYSCRASIAS
   Eugene Kaplan, M. D.
   Detroit

10. Pediatric Pathology
John A. Bigler, M. D.
Chicago
Joseph Boggs, M. D.
Chicago

11. Nature, Recognition and Management of Neuromuscular Disabilities in Children
Meyer A. Perlstein, M. D.
Chicago

Sunday Evening, Oct. 19, 1952, 8 p.m.

SECTION MEETING

Section on Mental Growth and Development

Milton J. E. Senn, M.D., *Chairman*

Personality Development in Infancy and Childhood
Margaret Girard, M.D.
Chicago

Problems Arising Around Normal Development
Julius Richmond, M.D.
Chicago

Emotional Management of the Hospitalized Child
William S. Langford, M.D.
New York City

All members are invited to attend this Sunday Evening Section Meeting.

MONDAY, OCT. 20

Morning Session

SYMPOSIUM

Hydrazine Derivatives of Isonicotinic Acid

1. Experimental Chemotherapy and Resistance
Emanuel Grunberg, M.D.
Hoffman LaRoche Laboratories
Nutley, N. J.
2. Pharmacology
J. C. Burke, M.D.
E. R. Squibb Laboratories
New Brunswick, N. J.
3. Clinical Experiences and Evaluation
Bret Ratner, M.D.
New York City

PAPERS

1. Progress in the Care and Treatment of Children With Disseminated Cancer
Sidney Farber, M.D.
Boston
2. Surgical Treatment of Inter-Auricular Septal Defects
Robert E. Gross, M.D.
Boston

Afternoon Session

SYMPOSIUM

Surgical Problems in Childhood

Chairman, Willis J. Potts, M.D., Chicago

1. Pectus Excavatum (Funnel Chest) - A Medical or Surgical Problem
Alexander H. Bill, Jr., M.D.
Seattle
3. Treatment of Undescended Testicle
Orvar Swenson, M.D.
Boston
3. Treatment of Undescended Testicle
Everett C. Koop, M.D.
Philadelphia
4. Bronchiectasis
Frederick R. Wilkinson, M.D.
Toronto
5. Bleeding from the Bowel
Henry W. Hudson, Jr., M.D.
Boston
6. Intussusception
Oswald S. Wyatt, M.D.
Minneapolis

The indications for surgery and the proper time for surgery will be emphasized. Where methods of treatment are controversial, all viewpoints will be discussed.

PAPERS

1. Incidence and Progression of Allergic Syndromes in Children
L. G. MacKenney, M.D.
Buffalo, N.Y.
2. Use of Opaque Media in Cardiac Diagnosis
Presentation accompanied by moving pictures
Richard Melzer, M.D.
Rochester, N.Y.

Evening Session—8 p.m.

Joint meeting of the American Academy of Pediatrics and National Safety Council

Presiding: George M. Wheatley, M.D., Chairman of Committee on Accident Prevention, American Academy of Pediatrics.

PART I

PROGRESS REPORT OF PILOT STUDY OF CHILDHOOD ACCIDENTS
William Langford, M.D.
New York City

PATHOLOGICAL STUDIES CONCERNING THE NATURE OF "MECHANICAL SUFFOCATION" IN THE YOUNG
Sidney Farber, M.D.
Boston

PART II

COMMUNITY ACTION FOR CHILD ACCIDENT PREVENTION
(A Dramatization)

Note: National Safety Congress will be held in Chicago, Oct. 20-24.

TUESDAY, OCT. 21

Morning Session

PAPER

PEPTIC ULCERS IN CHILDHOOD
Bertram Girdany, M.D.
Children's Hospital
Pittsburgh

SYMPOSIUM

EFFECT OF ABNORMAL STATES ON RENAL PHYSIOLOGY
Chairman: Mitchell I. Rubin, M.D., Buffalo, N.Y.

1. RENAL CLEARANCE METHODS IN THE STUDY OF RENAL PHYSIOLOGY
   Homer Smith, M.D.
   New York City
2. RENAL CONTROL OF ELECTROLYTE AND WATER METABOLISM
   Robert W. Berliner, M.D.
   National Institute of Health
   Bethesda, Md.
3. ETIOLOGY AND MANAGEMENT OF OLIGURIC STATES
   Stanley Bradley, M.D.
   New York City
4. IMMATURITY OF RENAL FUNCTION IN EARLY LIFE
   Mitchell I. Rubin, M.D.
   Buffalo, N.Y.

Luncheon Meeting—12 Noon to 2 p.m.

1. Committee on School Health—John L. Reichert, M.D.
2. Committee on Medical Education—Lee Forrest Hill, M.D.
3. Committee on Mentally and Physically Handicapped Children—George F. Munns, M.D.
4. Committee on Fetus and Newborn—Wyman C. C. Cole, M.D.
5. Committee on Accident Prevention—George M. Wheatley, M.D.
6. Committee on Public Relations—Oliver L. Stringfield, M.D.

Afternoon Session

SYMPOSIUM

HEARING, SPEECH AND READING DIFFICULTIES IN CHILDREN
Chairman: John E. Bordley, M.D., Baltimore

1. HEARING DISORDERS
   William Hardy, M.D.
   Baltimore
   Miriam Pauls, M.D.
   Baltimore
2. SPEECH DISORDERS
   Harlan Bloomer, M.D.
   Ann Arbor, Mich.

PAPERS

1. RECURRENT SWELLING OF PAROTID GLAND
   Stephen Royce, M.D.
   San Marino, Calif.
   Rustin McIntosh, M.D.
   New York City
2. DEFICIENCIES OF SPECIFIC PLASMA PROTEINS IN THE PATHOGENESIS OF DISEASE
   Charles A. Janeway, M.D.
   Boston
3. RETROLENTAL FIBROPLASIA IN PREMATURE INFANTS AND KITTENS
   W. R. Hepner, Jr., M.D.
   Galveston, Texas

Evening Session—To be held at the Museum of Science and Industry—8 p.m.

PANEL DISCUSSION

AUDIOVISUAL AIDS TO EDUCATION

Major Lennox Lohr, Director of the Museum of Science and Industry

David S. Ruhe, M.D., Director, Medico-Audio-Visual Institute

Mr. Tom Jones, Professor of Medical and Dental Illustration, University of Illinois

Attendance at panel is limited to 1,000.

Conducted tours of the Museum will be provided for the ladies.

Transportation to and from the Museum will be furnished.

WEDNESDAY, OCT. 22

Morning Session

SYMPOSIUM

NEUROLOGICAL CONDITIONS IN CHILDREN

Chairman: Randolf K. Byers, M.D., Boston

1. CONVULSIVE DISORDERS IN CHILDHOOD
   Fred Gibbs, M.D.
   Chicago
2. INFECTIONS OF THE CENTRAL NERVOUS SYSTEM
   Hattie E. Alexander, M.D.
   New York City
3. STUDY OF CEREBRAL PALSY
   Bronson Crothers, M.D.
   Boston
4. SURGICAL CONDITIONS OF CENTRAL NERVOUS SYSTEM
   Donald Matson, M.D.
   Boston

Presentation of Scientific Award Papers

MEAD JOHNSON—FIRST AWARD

GROWTH REQUIREMENTS OF BACTERIAL VIRUSES

S. Cohen, M.D.
Philadelphia

MEAD JOHNSON—SECOND AWARD

ELUCIDATION OF THE PATHOGENESIS AND TREATMENT OF CONGENITAL MEGACOLON

O. Swenson, M.D.
Boston

D. E. Neuhauser, M.D.
Boston

BORDEN AWARD

CARE OF PREMATURE

Julius Hess, M.D.
Chicago

Afternoon Session

ANNUAL BUSINESS MEETING FOR MEMBERS OF THE ACADEMY ONLY

Wednesday Evening—Annual Banquet

THURSDAY, OCT. 23

Morning Session

SYMPOSIUM

BASIC MECHANISMS IN ALLERGIC DISEASES

Chairman: Bret Ratner, M.D., New York City

1. ANTIGEN-ANTIBODY MECHANISM IN ALLERGY AND THE MECHANISM OF ANTIBODY FORMATION
   T. N. Harris, M.D.
   Philadelphia
2. PHYSIOLOGICAL MECHANISMS OF ANAPHYLAXIS AND ALLERGY
   Bret Ratner, M.D.
   New York City
3. PATHOLOGY OF THE ALLERGIC AND COLLAGEN DISEASES
   Milton G. Bohrod, M.D.
   Rochester, N.Y.
4. THE MECHANISMS OF ALLERGY TO DRUGS AND ANTIBIOTICS
   A. Rostenberg, Jr., M.D.
   Chicago

Afternoon—Clinical Conferences

Clinic No. 1—Children's Memorial Hospital

Clinic No. 2—Children's Division, Cook County Hospital

Clinic No. 3—Bobs Roberts Memorial Hospital for Children

Clinic No. 4—Sarah Morris Hospital for Children, Michael Reese Hospital

Round Table Discussion

THE PROBLEM OF MENTAL DEFICIENCY IN CHILDREN

HERMAN YANNET, M.D., Southbury, Conn., *Chairman*
M. A. PERLSTEIN, M.D., Chicago, and ALBERT J. SHELDON, M.D., Santa Ana, Calif., *Secretaries*

Chairman Yannet: Mental deficiency may be defined as an interference with the development of intellectual capacity resulting in social inadequacy. This may be so severe as to necessitate complete custodial care indefinitely; it may be so slight, that a simple change in environment or program may allow for relatively normal community activity with minimal to no supervision. For these different degrees of disability a wide variety of terms have been used. In decreasing order of disability, the terms most frequently employed including their definitions in terms of intelligence quotients are as follows:

1. Borderline: I.Q. 70-80
2. Moron or high grade: I.Q. 50-70
3. Imbecile or middle grade: I.Q. 20-49
4. Idiot or low grade: I.Q. 0-19

Such terms as feeblemindedness and mental retardation are generally used interchangeably for mental deficiency.

Obviously, not all children failing to adjust socially or follow normal paths of development are so because of basic mental deficiency. Certain other conditions, either superficially or strikingly resembling mental deficiency states, must be differentiated. These latter conditions require a different and sometimes highly specialized therapeutic approach and any considerable delay in their recognition may adversely affect subsequent adjustment. The most common of these conditions include the following which are briefly described:

1. Delay in Educational Maturation: There is considerable variation in the time at which children of normal intellectual capacity reach the stage at which they properly react to the usual educational procedures, normally introduced at about 6 years of age. This so-called period of "educational readiness", for want of a better term, includes many aspects such as attention span, personal relations and socialization status, and may occasionally be delayed 2 or 3 years. This makes it difficult if not impossible for the child to adequately profit from the usual early educational experiences. If such a cause for delayed school progress is erroneously attributed to basic intellectual deficiency and so handled, the child may be more or less handicapped as regards future emotional development and adjustment. Adequate psychologic study readily allows for proper recognition.

2. Specific Defects: Gross visual and auditory defects need no special discussion. Minor degrees including high tone deafness occasionally present diagnostic problems. Less common are visual defects of cortical nature such as congenital or acquired word blindness. Also aphasias, which are language disabilities, due to cortical abnormalities, are being recognized with increasing frequency and represent important conditions to be differentiated since their treatment and handling differ radically from that of the mental defective. Whether the aphasia is primarily expressive or receptive in type, its presence may be suspected by the striking disparity between the lack of verbal accomplishment and the relatively normal levels of motor and social aspects of the child's development. Confirmation is obtained by complete psychologic evaluation.

3. Psychogenic Factors: Deep-seated emotional disorders and accompanying personality and behavior disturbances may seriously interfere with the normal processes of intellectual development to the extent that the resulting clinical picture may occasionally be mistaken for a fundamental intellectual deficiency. In such cases, as well, psychologic study including projective technics will usually suggest the basic cause for the developmental difficulty.

4. Psychotic States: While relatively rare, psychotic states in comparatively young children do occur, and because of the bizarre and unexpected behaviorisms may superficially resemble the more severe grades of mental deficiency. In most cases the history of a relatively normal early development in all spheres merging almost imperceptibly and without physical cause into grossly abnormal

behavior patterns associated with the tendency to lose most of the already acquired verbal accomplishments and to withdraw from personal contacts suggest the diagnosis, in many cases. Other clinical manifestations of this syndrome in children do occur, however, and prolonged observation is frequently necessary for differentiation.

Etiologic Classification

Factors or conditions responsible for the occurrence of mental deficiency may be operative during any phase of the prenatal period, at birth or during postnatal life. The relative importance of these 3 periods in determining the incidence of mental deficiency has not been adequately estimated for the general population at large. Data is, however, available in reference to institutionalized defectives. Such data, unfortunately, is by no means of random nature since admissions to mental defective institutions is dependent primarily on social considerations obviously not directly related to etiologic implications. For instance, one type of mental defective, the familial moron, is genetically determined and almost invariably springs from parents who are either themselves defective or at least of inferior or borderline intelligence. As a result of their limited intelligence and lower economic position, the community status of such families tends to accentuate the early social inadequacy of the offspring especially during early school years, and increases the likelihood of institutionalization. Thus the importance of genetic factors would tend to be over-emphasized in public institution statistics. Bearing this in mind, the data obtained at the Southbury Training School may be presented as representative of institutional experience. Thus, of approximately 2,000 admissions, in only 3% could injuries during birth be implicated. In 6%, postnatal factors such as central nervous system infections, trauma, immunizations, etc., were noted as causative agents. Over 90% were due to etiologic agents operative during the prenatal period. And, approximately half of these were definitely hereditary in nature. Of the remainder, most of the etiologic factors were either completely unknown or, like mongolism, of controversial nature.

It is possible at present to identify, either in etiologic groupings, or as recognizable clinical syndromes approximately 70% of all mental defectives. It is not the intention of this discussion to exhaustively present the various clinical conditions and syndromes with which mental deficiency is associated. Limitations of time make it necessary to simply indicate and briefly describe the pertinent details pertaining to the more common conditions.

Prenatal States

1. Genetic: As previously indicated, genetic factors play an exceedingly important role in the etiology of mental deficiency. It is possible to recognize various genetically determined conditions without too much difficulty even when no other similar cases have occurred to raise this question. The importance of early diagnosis of a genetically determined disease and some knowledge of the nature of the genetic transmission for the proper advice to parents needs no elaboration.

A. The familial type of mental defective, practically always of moron level, represents over 30% of the institutionalized population and close to 75% of the moron population at large, and is of considerable sociologic importance. The diagnosis can be made by the presence of a somewhat similar degree of mental retardation in other siblings, and defective or inferior intelligence in one or both parents. As a rule there are no clinical abnormalities of a neurologic nature and the configuration of head and body are not remarkable. The type of genetic transmission suggests a polygene mechanism not unlike that operative in the transmission of normal intelligence. Thus, from various reported studies, it has been found that when both parents are mentally defective, only 4% of the offspring are of average intelligence, the remainder being either of borderline or moron defective levels. When one parent is of moron and the other of borderline intelligence, offspring of average intelligence increase to 10%. When both parents are of borderline intelligence then about 28% of the offspring are of average normal levels and of the remainder, one-fifth are of moron level, and four-fifths, borderline. When one parent is normal and the other of borderline level, the incidence of moron defective levels is only 3% in the siblings, while 64% are normal and 33% are borderline. The familial moron represents one of the most important aspects of the entire mental deficiency problem primarily because of their numbers; and also because it is in this group that community failure in supplying specialized adequate education and training is particularly unfortunate. The relatively inadequate parents compound the community neglect, frequently resulting in serious antisocial behavior.

B. Phenylpyruvic oligophrenia was first described by Folling in 1934. It is a form of mental deficiency transmitted by a single autosomal recessive factor. Clinically it is characterized by a severe degree of mental defect, 80% being in the idiot or low imbecile levels, although in rare cases a borderline or dull normal level is encountered. There are no specific neurologic findings. The majority are poorly pigmented, over 80% being blond and blue-eyed. The metabolic defect is basically an inability to metabolize the amino acid, phenylalanine, presumably due to the absence of a specific enzyme. As a result, this amino acid accumulates in the blood reaching relatively high values. Before being excreted in the urine, it is presumably deaminized by the kidney, and appears as phenylpyruvic acid. This substance is easily identified by the addition of a few drops of 10% ferric chloride solution to previously acidified urine. A deep green color appears when phenylpyruvic acid is present. It can be found in very young infants as soon as milk is taken in reasonable quantities. The test in young infants can be carried out by the addition of the ferric chloride solution to freshly voided urine on the diaper. Although the absence of the specific enzyme prevents the metabolism of the phenylalanine, this amino acid can be normally incorporated into the body proteins. This has been shown by demonstrating normal levels in muscle and brain tissues examined at post mortem. There are no specific pathologic changes in the brain although considerable architectual distortion is present in the various cell layers. There is, as yet, no explanation for the mechanism responsible for the mental deficiency. In view of the fact that there is no obligate relationship between the degree of metabolic defect and the severity of the mental deficiency, it is unlikely that nutritional manipulation could in any way influence the course. Investigations along these lines have as yet been without significant results. There is the suggestion that the mental deficiency and the metabolic anomaly may be due to separate functions of the same gene or of 2 closely related genes appearing together but having possible differential expressions. Phenylpyruvic oligophrenia occurs in about 1% of institutionalized defectives. It is estimated that 1 to 2% of the general population may be carrying this abnormal gene.

C. The term "congenital ectodermoses" covers 3 closely related conditions, namely, tuberous sclerosis, neurofibromatosis and cerebral angiomatosis. Genetically they have been considered as Mendelian autosomal dominants with extreme variability in expression. Because of this, especially for the first 2 conditions, the clinical pictures are extremely variable. Mental deficiency is only one of the manifestations and occurs in only a small percentage of those exhibiting evidence of carrying the abnormal gene. Among the mental defective population, tuberous sclerosis is the most common of the 3. In very young infants, delay in development may be the only presenting finding. Usually, however, rather characteristic skin lesions are also present during early infancy or appear soon thereafter. These consist of slightly raised, small, pinkish white soft lesions first seen on both cheeks, and occasionally scattered over the trunk. These pathologically are fibroangiomata, the intensity of the pink or red color depending on the degree of angiomatous involvement. Another finding often seen in these young infants is the rather typical mulberry-like retinal tumor or phakoma. As the child grows older, other phenomena appear. These include sebaceous adenoma, especially at the naso-labial folds, intracranial calcification most often around the ventricles, and extracerebral neoplasia. Convulsions may be an early manifestation or may appear later. All degrees of mental defect may be seen, and when present is usually not progressive.

Neurofibromatosis is so closely related to tuberous sclerosis as regards its manifestations in infancy and childhood as to suggest a unitary genetic cause. In some children, features ordinarily described for either of these conditions may appear simultaneously. The neurofibromata may vary from the smallest, barely perceptible cutaneous growths as described above to grotesque overgrowths in limbs resulting in elephantiasis.

Cerebral angiomatosis (Sturge-Weber) is less closely related to the preceding conditions although bearing some superficial similarities. It is characterized by extensive cutaneous hemangioma of the face, forehead and scalp usually on one side, associated with angiomatous neoplasm on the cortex. Probably because of pressure of the vascular tumors, the underlying cortex undergoes superficial necrosis and early calcification. This results in characteristic radiographic findings of skull examinations consisting of serpentine calcified areas that tend to follow the cortical gyri. Unlike the calcification in tuberous sclerosis which rarely appears before the seventh or eighth year, I have seen the typical x-ray findings in the skulls of children with cerebral angiomatosis soon after birth. Mental deficiency is relatively uncommon and when it does appear is usually of the moron level. Practically all develop some manifestation of convulsive disorder.

D. Hereditary idiocy, due to an autosomal recessive gene, unlike the preceding conditions, has no other significant finding upon which to base a diagnosis except for a severe degree of mental defect appearing in 2 siblings and unexplained by other causes. There are no abnormal neurologic findings. Fortunately it is rare. Its importance stems from the inability of the physician to exclude it as a diagnosis in the case of the severely retarded child born to normal parents without adequate explanation.

E. Heredo-degenerative cerebral diseases may involve primarily either the white matter or the ganglion cells. They include a large variety of clinical conditions that in only a small number of cases can be differentiated during life, especially in infancy. Among the ganglion cell degeneration variety, Tay-Sach's disease and gargoylism are the most common. These are well described in many neurologic and pediatric texts. The white matter degenerative diseases are even more confusing in their terminology, and cover a wide variety of pathologic states that seem to have been described and named on the basis of isolated family studies, and variable periods of onset. These include the cerebral scleroses of Pelizaeus-Merzbacker, Scholz, Krabbe and others. Both the ganglion cell and white matter degenerative diseases are genetically determined and usually behave as autosomal recessives. They presumably represent metabolic defects of highly specialized enzymatic nature. Their importance in our discussion rests on the fact that delay in development may represent the first clinical manifestation of the condition in the very young child.

F. Muscular dystrophy of the childhood type, also described as pseudohypertrophic muscular dystrophy, is associated with mild degrees of mental deficiency in a few cases. The nature of the relationship between the muscular dystrophy and the cerebral malfunction is not understood. Genetically, the condition is probably a sex-linked recessive, which is practically confined to males.

G. Primary microcephaly is a distinct condition genetically determined and transmitted as a Mendelian autosomal recessive. It should be differentiated from a wide variety of other conditions either genetic or acquired in which diminution in head circumference is found. These include prenatal infections, degenerative diseases, birth traumas and congenital cerebral palsy. The appearance of the head is characteristic. The circumference may only be slightly decreased; the major diminution is in the cerebral volume due to an extremely low cranial vault. The forehead is strikingly sloped backwards. The facial bones, especially the mandible, age of normal size and by comparison appear enlarged. As a rule, there are no specific motor defects or neurologic abnormalities. The mental development usually is found in the high imbecile levels.

H. The craniostenoses include those conditions in which one or more of the cranial sutures prematurely close. The evidence in favor of including these conditions among those genetically determined is strong. The condition behaves irregularly, in some families as a Mendelian dominant, in others, as a recessive. The configuration of the skull will depend on the sutures involved. The 2 most common varieties are oxycephaly in which the coronal suture is affected, and the head is short rising to a blunt top; and scaphocephaly, affecting the sagittal suture and resulting in a narrow and long head. Bizarre shapes will result if more than one suture or parts of a suture are involved. Occasionally other parts of the skeleton are defectively developed. In some cases of craniostenosis, definite pressure symptoms appear. These include papilledema, optic atrophy, exophthalmos and increased cranial digitations. Mental deficiency may be present and may vary in degree from the most severe to a mildly involved moron state. There is considerable evidence to indicate that the mental defect, when present, is probably an associated symptom rather than secondary to the premature suture fusion. Regardless as to whether mental deficiency is a secondary phenomenon or not, however, operations designed to prevent the disfiguring effects are definitely indicates for cosmetic purposes at least, in many cases.

1. Hypertelorism is an uncommon cranial anomaly in which the eyes are widely separated and the root of the nose depressed. Varying degrees of mental deficiency may be associated. Basically, the configuration of the skull is due to the overgrowth of the small wings of the sphenoid, although other anomalies of development at the base of the skull are seen. There is no direct correlation between the degree of skull anomaly and the intensity or even the presence of mental deficiency since certain of these children may be of relatively normal intelligence. There is considerable evidence in the literature to indicate a genetic basis for this disorder. It appears to behave as an irregular dominant in some families and recessive in others. As in other conditions, mutations may explain the frequent sporadic appearances. Also of interest is the high incidence of congenital heart anomalies in this condition.

2. Infections: Prenatal infections as a cause of mental deficiency have recently been stressed. Although the whole story is far from told, we can only definitely recognize at present 3 distinct etiologic agents of any consequence. These include rubella, toxoplasmosis and congenital syphilis. In all 3, mental deficiency represents only one aspect of what may be a complicated clinical picture. Because the fetal infection with rubella virus occurs as early as the first trimester, the degree of abnormality both cerebral and otherwise is usually the most extensive. The clinical picture may be quite variable. When associated with the more severe degrees of mental deficiency, the clinical manifestations include microcephaly with or without motor defects, cataracts, congenital heart disease and deaf-mutism. Prenatal infection with toxoplasma apparently occurs later in pregnancy. Occasionally infection may take place in the paranatal period. The presenting symptoms are variable depending in part on the time of infection. Mild hydrocephalus or microcephalus usually with intracranial calcification, and almost always associated with bilateral chorioretinitis is the most common picture. The intracranial calcification is widely disseminated in the peripheral cortex, and tends to be granular in appearance. In this respect it greatly differs from the calcification seen in tuberous sclerosis which tends to be periventricular and conglomerate in appearance. Congenital syphilis is now a very rare cause of mental deficiency. In addition to the usual signs of congenital syphilis, in these children there is also neurologic evidence of central nervous system involvement including changes in the C.S.F. The mental defect is usually in the moron levels.

3. Irradiation: This is extremely rare clinically, and results from the application of therapeutic doses of x-ray or radium to the pelvis of a pregnant woman during the early months of gestation. Severe fetal cerebral malformations with symptomatic microcephaly and marked degrees of mental defect are the most common manifestations in the subsequently delivered infant. Considerable experimental work in animals has confirmed these observations. Eye and skeletal defects have also been produced in the experimental animals.

4. Isoimmunization: Maternal Rh or ABO isoimmunization may result in fetal cerebral damage. It is a relatively uncommon cause of mental deficiency, being responsible for approximately 1% of the institutionalized mental defectives. In addition to mental deficiency, the clinical manifestations include cerebral palsy, cranial nerve defects, convulsive disorders and aphasias. The degree of mental defect is variable. Motor defects, with or without mental defect, include hypertonic states, hypotonia, athetosis and ataxia either alone or in various combinations.

5. Miscellaneous Conditions:

A. Mongolism is one of the most common of classifiable conditions among mental defectives. It represents approximately 10% of institutionalized defective children. It occurs about once in every 500 to 700 births. It can be diagnosed at birth, although many times with difficulty, the condition having begun to differentiate very early in fetal life probably around the sixth to the eighth week. While the diagnosis requires the presence of the peculiar and characteristic skull deformity which results in the upward and outward slant of the eyes, the disorder is widespread. Associated anomalies include defective skeletal growth, cardiac abnormalities, congenital eye disorders, and many others. Mental defect is most commonly in the imbecile range and always present.

While there has been considerable research and discussion concerning etiology, no viewpoint has been generally accepted. For myself, the available evidence favors the hypothesis that the defect is basically genetic but that its expression is influenced by various environmental factors such as maternal age, hormonal deficiencies, local uterine abnormalities and others. If this is so, the possibility of prevention may lie in our ability to recognize and modify these environmental factors. As regards treatment, there is no good evidence that the expected course of the condition can in any way be beneficially influenced by any available medicinal therapy, endocrine or otherwise.

B. Cretinism probably represents the only endocrine disorder that seems to be specifically related to mental deficiency. While many other endocrine disorders can be found among defective children these are associated abnormalities rather than a direct cause of the mental state. So-called congenital myxedema or cretinism appears to be of 2 types which may have different pathogenic mechanisms, or may merely represent a matter of degree of thyroid deficiency. Although both types usually require a few months for recognition, in one, the administration of thyroid seems to completely correct the disorder and allow for subsequent normal development both physical and mental. In the other, thyroid may stimulate physical growth effectively but a completely normal child, particularly mentally, is not obtained. The etiology is not clear in every case. While genetic factors probably do play a role in some cases, sporadic examples are numerous, especially in this country and may be environ-

mentally determined. Obviously, thyroid is indicated in every case and early diagnosis should be sought.

C. Approximately 30% of institutionalized mental defectives can be recognized as being prenatally conditioned but are completely devoid at the present time of differentiating characteristics that would allow for accurate classification. To this large group, the term "undifferentiated" is applied. Its size indicates the tremendous gap in our knowledge of prenatal injurious factors.

Natal and Postnatal Conditions

As was indicated earlier, on the basis of institutional statistics only 9% of mental deficiency states are due to factors operative at birth or during infancy. Diagnosis is usually readily made at the time of the acute condition. However, etiologic diagnosis made in retrospect many years after birth presents considerable difficulty and is frequently unreliable. The criteria demanded for retrospect diagnosis varies considerably in different clinics and by different investigators. This undoubtedly explains the striking discrepancies in the incidence of acquired factors in the various studies which have appeared. It is unnecessary to do more than list these possible factors which should be considered in reaching an etiologic diagnosis.

1. Birth trauma includes various injurious mechanisms such as cerebral hemorrhages, thromboses especially of the cerebral sinuses, subdural hematomas, both unrecognized and those unsuccessfully treated, and prolonged asphyxia, either due to delay in initiation of adequate pulmonary exchange or interference with umbilical blood supply.

2. Postnatal conditions include infections of the central nervous system either suppurative or nonsuppurative including postimmunization reactions; acute cerebral trauma resulting from accidental falls and head injuries; cerebral vascular thromboses arterial or venous, many at present spontaneous and unexplained, a few secondary to severe infantile dehydration; spontaneous intracranial hemorrhages on the basis of ruptured congenital aneurysms or mycotic aneurysms; asphyxia associated with drowning accidents, gas poisonings including anesthesia accidents and acute tracheobronchial obstructive conditions; certain central nervous system poisons accidentally ingested, and probably others.

Treatment

A. Organic Methods: The last few years has witnesed an increasing interest in possible organic methods for stimulating or accelerating the mental development in established states of mental retardation. These have included the use of large doses of glutamic acid, a preparation of calf pituitary for mongoloid children, excess vitamin B_{12}, and a surgical procedure (cerebral revascularization) designed to increase cerebral blood flow. Two of these have been adequately tested under reasonably well controlled conditions and have failed to live up to the original expectations (glutamic acid and cerebral revascularization). It is likely that their employment for the original purpose of improving basic intellectual status will diminish and soon disappear. Too few reported results are available for the remaining methods on which to base any conclusions. On the available evidence my reaction is pessimistic as to obtaining eventual significant results. It is heartening, however, to note the increasing interest being given to the direct organic therapeutic approach to the problem of mental deficiency.

B. Educational and Social Procedures: The foundation of treatment, using the term in its broadest sense, for mental defectives still remains based on the following 3 fundamentals:

1. Specialized education consistent with the intellectual capacity.
2. Industrial training to prepare the individual for useful work if possible, and
3. Providing, at all times if necessary, an environment that will allow satisfactory personality and emotional development.

While children of practically all degrees of defect except for the most seriously retarded could profit from such a program, it finds its greatest application to the so-called "trainable group." These represent children with intellectual capacities in the ranges of the high level imbecile, the moron and the borderline grades. Under ideal conditions, the proper facilities and environment would be supplied by the home, public schools and community. Unfortunately, these conditions are not always available, especially in the smaller communities. It should be one of the responsibilities of the medical profession to help stimulate the local school systems to make adequate provisions for the care and training of these children. As is true for the normal child, the trainable defectives are best handled in their own homes. This is particularly important during the early years of childhood.

The adequacy of the early home and school experiences will in great part determine the success of later industrial and community adjustment. Studies in communities supplying such specialized educational facilities have indicated the excellent prognosis to be expected. (Trainable mental defectives: Comment on prognosis, J. Pediat. **37**: 816, 1950.) The institutionalization of the trainable defective should be necessary in only a small proportion of these cases. The indications should include one or more of the following: (a) a home situation that is grossly undesirable; (b) a community completely devoid of facilities; (c) the development of serious behavior or personality difficulties in the child. Of these, the most common is unsatisfactory home environment, most frequently due to inadequate parental adjustment and understanding. Much of the subsequent behavior difficulties of the occasional child so exposed can be traced to this factor. Although early parental training and advice will partially solve some of the problems and reduce the need for institutionalization, this is not always possible. It is, of course, apparent that should it be necessary to remove such a child from the home for institutional care, one must at least assure himself that a suitable educational and training program will thereby be made available. Too many of our state schools for mental defectives, as well as many of the private schools, fail strikingly to supply these needs. Another possibility to be explored in these cases, prior to institutionalization, is the use of suitably situated foster homes, in communities with adequate facilities. Our experience repeatedly confirms the oft repeated observation that the finest of residential training schools and institutions is still inferior, as a child raising agency, to adequate homes, personal or foster.

The other category of mental defectives, the custodial, includes those children whose mental capacity will make it impossible to attain a condition of even partial self support in the community regardless of the highest level of training and care. These include all of the idiot level, and most of the imbecile or middle grade defectives. Approximately 20 to 25% of all defectives fall into this category. Unlike the trainable group, a reasonably large number of these children can be recognized as custodial almost from birth: for example, the mongoloids and the primary microcephalics. The problem for physicians, as regards planning for future care, and parental advice, will therefore present itself either soon after birth or during infancy. Moreover, the expected high mortality rate of preantibiotic days in these children, which tended to encourage procrastination on the part of the physician as regards discussion of future care with parents, has been strikingly reduced. While the parents will and should make the final decision, it is the responsibility of the physician to present all the facts in such a way that the parents' decision will be based on real understanding. What are these facts? They will be discussed using the mongolian child as an example, since this represents the most common custodial type that can be recognized soon after birth; and from 3 points of view, namely, the child, the family, especially the mother, and economic considerations.

1. The mongoloid infant will undoubtedly receive better care from the exclusive attention of its mother than it can expect in any institution. Also, as is true for the normal child, the mongolian child may be expected to profit considerably, developmentally speaking, from the security, affection and attention afforded by its parents and family during the early years spent in its own home. Any possible benefits, as they may affect the parents or family, to be expected from removing the mongoloid infant from its home soon after birth or during early infancy, should be weighed against these considerations. As the mongolian child grows, and its deviation from the normal becomes increasingly evident, the possibilities for childhood companionship and play become increasingly limited in his own home. Thus there comes a time when what the mongolian child gains from home care is greatly overshadowed by what he misses in the opportunities to explore human relationships and develop at his own rate. A point of diminishing returns is almost invariably reached with adverse effects on both the child and family. The time when this point is reached is quite variable, depending on the home environment and the degree of developmental retardation exhibited by the child. In some, it may be at 2 years or earlier. In others, it may not be before 6 or 8 years of age. If the family is adequately educated to this fact, they can usually determine this point for themselves. The institutionalization of the child at this time becomes advisable for his own sake. With few exceptions, a family, especially the mother, who has been informed of the plan from early life and has been a partner in reaching a decision, has little difficulty in adjusting to the removal of the child from the home to another environment more suitable for the child's emotional well being.

2. There are only 2 valid reasons that a physician can give for advocating the removal of the mongolian child from the home soon after birth. First is the possible adverse effects on the family, especially siblings, in having a custodial problem in the home. Second is the possibility that the

mother or family will become so emotionally attached to the child that they will not be able to allow the child to leave the home when the proper time is reached. Experience has shown that both are valid reasons; but, I believe they apply to only a small percentage of cases. Here again, the physician, in frank discussion with the family, can help decide jointly if such possibilities might be reasonably expected to occur in spite of whatever psychotherapeutic help the physician can give through his contacts with the family. It may be mentioned as well that, from my own experience, I have no reason to believe that the emotional development of normal children is adversely affected by the presence of a custodial type of defective child in the properly oriented family.

3. We may reasonably expect that at no time will there be enough public institutions to care for all custodial children of this kind from early infancy. In the absence of available public facilities, advice to remove these infants from the home makes it necessary to use private institutional care. Should any considerable time elapse before a bed is available in a state institution, the cost to the family may represent a considerable burden. Only if a physician can convince himself and the family that the financial sacrifice is commensurate to the benefits to be derived from such a procedure should the expenditure be advised.

C. Sterilization: Sterilization is an important auxiliary procedure in the management of mentally defective individuals, especially females in the trainable category. Although it has eugenic implications, its greatest value lies in the social sphere as regards the over-all problem of mental deficiency. The prevention of parenthood in the defective is indicated socially on 2 grounds. First, the mentally defective individual will make, as a rule, a poor, ineffectual parent regardless of the mental status of the child. Second, the problems of pregnancy in the unmarried and parenthood in the married are frequently responsible for adversely affecting the social adjustment of the defective in the community necessitating return to the institution, or requiring an original commitment in a previously well adjusted situation.

Pediatrics

VOLUME 10 AUGUST 1952 NUMBER 2

SPECIAL SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

"A forum where discussion could be free, intelligent and continuous."

PAUL A. HARPER, M.D., *Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

COMMUNICATIONS FROM NELSON K. ORDWAY, M.D., AND BRUCE W. EVERIST, M.D.

TWO communications are presented in this issue: the first is from Dr. Nelson K. Ordway, Professor of Pediatrics at Louisiana State University School of Medicine; the second is from Dr. Bruce W. Everist, senior pediatrician to the Green Clinic at Ruston, La.

DEAR DR. HARPER:

I am moved to write you because I believe it is important that the facts I am going to relate be generally known to pediatricians. Sooner or later every mentally retarded child comes to the attention of a physician. The cost of care for these children, particularly the burden of expense involved in their supervision at "schools" on a part- or full-time basis, is a permissible deduction as medical expense on Federal Income Tax returns. The propriety of this deduction is not generally known either to physicians or the parents of their patients. The pertinent language of the Internal Revenue code bearing on this problem is as follows:

"Sec. 23 (x). The term 'medical care,' as used in this subsection, shall include amounts paid for the diagnosis, cure, mitigation, treatment or prevention of disease, or for the purpose of affecting any structure or function of the body (including amounts paid for accident or health insurance.)

"Reg. 111, Sec. 29.23 (x)-1. Allowable deductions under section 23 (x) will be confined strictly to expenses incurred primarily for the prevention or alleviation of physical or mental defect or illness."

With a thorough understanding of the likely areas of difficulty in interpretation of the term, "medical care," by non-medical persons, the following letter was sent to the

local Collector of Internal Revenue by the president of the board of a local private school for exceptional children. The last paragraph was included in order that the request would not be set aside as moot on the grounds that it did not seek a ruling in any specific case.

February 9, 1952

Collector of Internal Revenue
Customhouse
New Orleans, Louisiana

DEAR SIR:

"I request confirmation that payments made to the Louise S. Davis School for the care, treatment, and management of children and young adults suffering from mental deficiency based on organic brain disease or emotional disturbance, or a combination of such conditions, may be treated as medical expenses within the meaning of Sec. 23 (x), I.R.C. and Reg. 111, Sec. 29.23 (x)-1.

"The Louise S. Davis School, in common with all institutions of this sort, is designated a 'school' to remove, in part at least, the stigma attached by many lay persons to mental institutions. It is a specialized hospital with school facilities, where the prime object is treatment, which includes specialized teaching as a therapeutic measure and continues throughout the entire year. The Louise S. Davis School thus differs fundamentally from public and private schools for mentally normal children, since the educational aspect is only one phase of a comprehensive treatment program. Neither is its curriculum comparable to the ancillary educational program in institutions for children with chronic 'physical' illness, such as tuberculosis, rheumatic fever, or poliomyelitis. The children receiving care at the Louise S. Davis School cannot properly be looked upon as pupils but should be considered as 'out-patients' or 'in-patients,' depending on whether part- or full-time treatment is necessary.

"Mental deficiency is most commonly a developmental defect, but it may appear also as a sequel to brain injury or infectious disease. Unable to keep up with normal persons, feeble-minded children are unusually susceptible to emotional disorders requiring psychiatric therapy. They cannot be cured, but treatment is both mitigative and preventive, with the aim of promoting optimal cerebral function within the limits set by their disease. Without treatment these children often become dangerous both to themselves and to society.

"Specific treatment for feeble-minded persons falls within the following categories:

"1. Training in the best possible use of the patients' limited faculties for care of their creature needs and adjustment to their social environment, e.g., through speech training, promotion of coordinated muscular activity, and exploitation of relatively superior traits. This is achieved through personalized attention to individuals in more or less homogeneous groups.

"2. Prevention of emotional maladjustments through living and expert training in an environment in which subjects compete with their intellectual peers, rather than with children of normal mental endowment.

"3. Mitigation of the effects of many disorders commonly associated with mental deficiency (such as overactivity, epilepsy, and cerebral palsy), through speech training, corrective physical education, drug therapy, etc.

"The Louise S. Davis School offers treatment of the nature outlined above to children accepted following a physician's recommendation. The School is directed by a person specially trained in the management of feeble-minded children. It is operated by a lay board, which acts with the advice of a medical council of 4 physicians.

"The writer has a personal interest in the ruling of your department in this vital matter, inasmuch as he has a son who is being treated at the Louise S. Davis School."

The letter was promptly forwarded to the Commissioner of Internal Revenue in Washington, and within a little over two weeks the following reply was sent directly to the school.

It:RP:TR
JAC-6

Office of Commissioner of Internal Revenue

The Louise S. Davis School
5005 Magazine Street
New Orleans 15, Louisiana

GENTLEMEN:

"Reference is made to your letter of February 9, 1952, addressed to the Collector of Internal Revenue, New Orleans, Louisiana, which was referred to this office for consideration and reply. You request a ruling as to whether the amounts paid to you by individuals for the treatment and care of their children, would constitute medical expenses within the meaning of section 23 (x) of the Internal Revenue Code and the regulations promulgated thereunder.

"The purpose of the Louise S. Davis School is to provide care, treatment, and management of children and young adults suffering from mental deficiency based on organic brain disease or mental disturbance, or a combination of such conditions. The institution was designated a 'school' to remove, in part at least, the stigma attached by many lay persons to mental institutions. The children receiving care at the school cannot properly be looked upon as pupils since the educational aspect is only one phase of a comprehensive treatment program, but should be considered as 'out-patients' or 'in-patients' depending on whether full or part time treatment is necessary. The admission to the school is dependent upon a physician's recommendation. The director of the school is a person specially trained in the management of feeble-minded children. It is operated by a lay board which acts with the advice of a medical council of four physicians.

"It has consistently been the position of the Bureau that the costs incurred by taxpayers for sending their children to a private school to receive special care and treatment designed to alleviate their physical, muscular, or nervous abnormality, and at the same time to receive the same kind of instruction and care usually given to children of their age in schools, is deductible as a medical expense under section 23 (x) of the Internal Revenue Code to the extent of the amount necessary to pay for such medical care and treatment. The balance, which pays for ordinary instruction and care as the children would require in any event, is not a medical expense. In such a case an apportionment is necessary and the taxpayers should submit with their returns evidence to establish the basis of the apportionment and its reasonableness.

"That portion of the expenses incurred by the individuals for maintaining their children at your school which pays for ordinary care and instruction is a question of fact

and must be determined by them. In computing their medical expense deduction, the individuals would be entitled to include only that portion of the expenses incurred for their children which represent expenditures primarily for and essential to the rendition of medical services."

One of the chief stumbling-blocks encountered when payments for institutional care are requested as a medical deduction, is the difficulty many lay persons have in understanding that mental retardation is an illness, and that its specialized care is indeed as truly "medical" as, let us say, orthopedic care of a child who has had poliomyelitis. The individual preparing his income tax return still has the task of proving to the local Collector of Internal Revenue that the "instruction and care" offered are indissoluble from the comprehensive treatment program as a whole; that they are neither "ordinary" nor "the same kind . . . usually given to children of their age in schools," and that the entire school program is "primarily for and essential to the rendition of medical services."

Collectors of Internal Revenue recognize the responsibility of the government as well as the obligations of the taxpayer, and are anxious to give the individual every possible advantage in the preparation of his return. They, like most other non-medical persons, have difficulty in understanding that mental retardation is a medical illness and that its treatment is anything more than ordinary education. The duty of the physician to the parent of a retarded child, therefore, may involve not only apprising him of this means of lessening to some extent his financial burden, but actually coming to his aid by explaining these matters, as only a knowledgeable person can, to the local Collector of Internal Revenue. Reference to the letter from the Commissioner of Internal Revenue quoted herein may be helpful.

(signed) NELSON K. ORDWAY, M.D.
New Orleans

DEAR DR. HARPER:

Dr. Myron Wegman reviewed a paper that I recently presented to a group of social welfare people and felt that it had some merit. He suggested that I send it to you for perusal and possible publication in your column, "The Pediatrician and the Public."

Forgive the informality with which this has been presented. There was no thought of publication when it was prepared and it merely reflects the opinion of a few local physicians who feel inclined to better themselves.

(signed) BRUCE W. EVERIST, M.D.
Ruston, La.

Medical services and the community, at first glance, would seem to concern primarily the relationship between the practicing physicians and the populace of a community; but of course there are obvious other agencies that are directly, or indirectly, associated with medical services; and the list is long. Perhaps we should place the practicing physician first, then state and local health departments, the United States Public Health Service, state supported charity hospitals, the World Health Organization, local and national health agencies such as the Red Cross, tuberculosis association, polio foundation, philanthropic organizations such as the Rockefeller and Russell Sage foundations, veterans' health services including veterans' hospitals, lay group hospitals such as the

Elks', such ancillary services as optometrists, midwives, pharmacists, podiatrists and, a very important concern to all of us, medical social workers. These services are only those that come to mind and there are others.

It would seem from this array of persons and agencies that any community's health should be completely assured. That there is a discrepancy between the facilities and the results would suggest that in some way we are either ineffectual or disorganized. I am sure it would be un-American, certainly unappreciated, and possibly criminal to say that we are ineffectual. Therefore, it must be that we are disorganized. This, I think, is true. In the past, a competitive breech divided these various services, and is still present, to a large degree. It becomes self evident that some correlating influence should be brought to bear to align our facilities into a united barrier against ill health.

Since I have had the temerity to list the practicing physician first, it seems to me that he should be charged with becoming an organizational axis. I believe it is the practicing physician's responsibility to attempt a more closely coordinated community health program out of the existing multitude of competing organizations. Most physicians are not prone to accept the role of moderator and I think their reasons in the past have been adequate. Most physicians shun headline agencies. Many have been too busy these past few years to accept the extra load of executive duties, and the majority of physicians tend to be strictly individualistic in their basic philosophies. Though these have been acceptable reasons in the past I think they no longer obtain. Until we can get the cooperation of all practicing physicians, their help, their knowledge of community needs and their abilities, we must of necessity remain disorganized. The doctor must be made to feel a part of, and a director for, these ancillary services. Only in small ways has this been done in the past.

I realize that there is no health utopia, but a nearly ideal community health program would seem to shape up something like this. First, form a central committee under the chairmanship of a responsible physician, and representative of all the agencies that are concerned with health in a community. This committee could act as an advisory board for the dispensation of thought, action and money. Then let the charitable contributions of all organizations be channeled into a central fund, which could then be used for whatever need appears in a community. Let this central committee or advisory board aid and abet the local and state health units and other governmental agencies so that there would be no overlapping and no waste motion. The central fund then could care for prophylaxis of tuberculosis; it could channel funds for maternal and child health, for poliomyelitis, immunization, visual and audiometric screening of school children, cancer detection, even hospitalization and treatment of the indigent who are acutely ill. The ramifications of such an organization within a community seem unlimited.

Certainly no two communities' health needs are the same. One community may have as its prime problem the custodial care of old people, and in an adjacent area maternal and child health may be a paramount need; in another community education for mental hygiene might have first call. I cannot visualize a community's health as a standardized, unchanging state; but rather as a dynamic, unpredictable and ever changing pattern. With a central committee these changing needs could be met, could be handled with the existing facilities.

Such a plan as I have outlined is not an impossible one. It is the plan that we in Lincoln Parish hope some day to follow. We have made a little progress. So far our

plan involves primarily pediatrics because the need in Lincoln Parish seemed greatest in this age group. All of our organizations for health services in our community are not represented but a majority are. We began by establishing a weekly, free clinic for children whose parents are unable to pay for medical services. This clinic is not sponsored by any one organization. It was conceived and staffed by practicing physicians in our community. Our professional help is donated by registered nurses. Our secretary gives her time free of charge. We have accepted funds from the Tuberculosis Association, Society for Crippled Children, the Poliomyelitis Foundation, the Salvation Army, civic clubs and local philanthropists. When it is at all possible the patients are asked to pay for the actual cost of medications. We have begun a screening program of audiometric testing of school children with an audiometer bought by one of the civic clubs of our largest town. This work is supervised by a practicing physician and registered nurses give their time in the general testing. The same thing is being done for visual screening. Our school health program is still in its infancy and it has been found to be one of the most difficult of our problems. When it was found that routine yearly physical examinations for all school children was an impossibility one school was chosen to try to establish a pattern for our future overall school health management. This also was conceived and put into operation by a practicing physician in our parish. With the aid of funds from the state government we have been able to make hospital beds available for acutely ill children of indigent parents. Some remedial surgery has been done free of charge with the cooperation of the surgeons, our local hospital, crippled children's society and state funds. Our educational program has not been a signal success but we believe that we are gradually convincing the solvent members of our community that until we have general good health all members of the community must suffer. Disease is no respecter of income or family background.

It has been gratifying to see some progress made in these few fields. We know that our community is still greatly in need of many other changes. Housing facilities for the lower income groups are a prime need, and the civic leaders of our community are working on this problem now. Sanitation is not of the highest order but constant effort is being exerted for improvement. We have a large population of old people whose incomes were adjusted to a pre-inflation era. We have no facilities for their custodial care. We have no mental health program. We have no organized well baby conferences and maternal health has been somewhat neglected. We have no facilities for exceptional children, either for institutional care or educational care or educational opportunities. All of these latter problems are a challenge to the medical services that are represented in our community. By correlating the various existing organizations we feel that a solution is within our grasp.

For the few things that we have been able to accomplish the most gratifying to me has been the willingness of the practicing physicians to cooperate and share in the program, and the altruistic attitude of the various ancillary medical services in combatting the obstacles to a common end. I believe it has given us all a feeling that we are beginning to be able to wash our own dirty linen with minimal outside aid. This concept of the local management of current health problems by cooperative enterprise seems fundamental. A positive, active approach by existing medical services to community deficits is not a step toward socialism but a workable means of impeding its spread.

TRENDS

By JOHN P. HUBBARD, M.D., *Contributing Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

THE PRESIDENT'S HEALTH COMMISSION LOOKS AT CHILD HEALTH

THE President's Commission on Health Needs of the Nation, appointment of which was noted in this column last February, has included within its broad assignment specific consideration of the health needs of children. On June 18 a panel of persons with special interest and experience in maternal and child health met in Washington with representatives of the Commission. A summary of the deliberations and recommendations of the panel will be submitted and discussed with the Commission itself on July 9.

The Panel on Health of Mothers and Children was made up of the following persons: Harriet Bartlett, Professor of Social Economy, Simmons College, School of Social Work, Boston; Leona Baumgartner, M.D., Assistant Commissioner in Charge of Maternal and Child Health, Department of Health, City of New York; Edward Davens, M.D., Chief, Bureau of Preventive Medicine, Maryland State Department of Health; Nicholson J. Eastman, M.D., Professor of Obstetrics, Johns Hopkins University School of Medicine; Martha M. Eliot, M.D., Chief, Children's Bureau; Mrs. John E. Hayes, Past President, National Congress of Parent Teachers Association; Albert E. Heustis, M.D., Michigan State Health Commissioner; John P. Hubbard, M.D., Professor of Public Health and Preventive Medicine, University of Pennsylvania School of Medicine; Mrs. Ethel Kirkland, State Midwife Consultant, Florida State Board of Health; Marion Murphy, Resident Lecturer in Public Health Nursing, University of Michigan School of Public Health; Mrs. Kate W. Smith, Social Worker, Turtle Mountain Indian Agency, Belcourt, N.D.; Mrs. I. H. Teilman, Chairman, Health Division, Fresno County Coordinating Council, Selma, Calif.; Myron E. Wegman, M.D., formerly Professor of Pediatrics, Louisiana State University School of Medicine, New Orleans, and now with regional office of World Health Organization, Washington, D.C.; Kent Zimmerman, M.D., Chief, Mental Health Services, California State Department of Health. Miss Elizabeth S. Magee, General Secretary of the National Consumers League and a member of the President's Commission, acted as Chairman.

The panel discussion was launched by Dr. Eliot who read a prepared statement which covered the subject in a very comprehensive manner and which drew extensively from the Academy's cooperative Study of Child Health Services. This statement was so inclusive and contained so much up-to-date information, that the suggestion was made that it should be published in full, either as a part of the Commission proceedings or separately. In any event, it would be premature to review the statement in detail at this time. The subject matter may, however, be noted briefly.

First, there was a review of the status of our child population, emphasizing—in this day when so much attention is being given to the aging population—the continuing high birth rate and the record-breaking number of the nation's children. In comparison with the increase in population over 65 years of age, the increase in population less than 5

years of age has been even greater, so that "we are growing younger faster than we are growing older." Attention was drawn, as in the Academy study report, to the progress in the care of children: the reduction of maternal mortality, infant mortality, mortality and morbidity in the pre-school ages, and the "extraordinarily successful" fight against many communicable diseases. The major part of the statement then proceeded to outline steps which may be taken to meet recognized existing needs and to achieve higher standards of maternal and child health. Specific consideration was given to the training of more health personnel of all kinds; to hospital services for children; to the quality and distribution of health services for mothers and children; to the special needs of handicapped and crippled children; to the economic barriers to medical care; to the need for more research, particularly evaluation studies of health programs and basic studies of the social and economic factors which influence child life; and finally certain special problems related to children in families of migrant laborers and to the children who are mentally or emotionally disturbed.

Many of the points presented by Dr. Eliot reappeared and came in for lengthy discussion as the panel proceeded throughout the rest of the day to consider the items in an agenda prepared by the Commission staff. This agenda included the following subjects (but let no one assume that the panel limited itself accordingly): contributions to comprehensive health care by maternity and child health programs; relationship between health services for mothers and children, and other family members and community life; deficiencies in the scope and quality of services, facilities, and the number, distribution and training of personnel with the question as to how these deficiencies may be overcome; the groups needing special consideration, such as families of migratory workers, families of service men, needs in special regions; and the need for research in many areas of child life.

This panel is only one of a large number called in by the Commission Chairman, Dr. Paul B. Magnuson, to assist the Commission and its staff in the staggering assignment to make a critical study of the nation's total health requirements and to recommend courses of action to meet these needs. Among the problems which the Commission was specifically asked to consider are: the current and prospective supply of health personnel; adequacy of training opportunities; availability of local public health services; amount and distribution of hospital, clinical and similar facilities; research; financing of medical care; the long range effect of requirements of military, civil defense, veterans and other public service programs upon civilian health resources; and the extent to which federal, state and local government services in the health fields are desirable.

In the relatively few months which the Commission was given to fulfill its assignment, it has met with some 25 to 30 panels, including experts in their respective fields from all over the country. Among the panels which have been heard in addition to that on the health of mothers and children are those on: general practice, specialization, group practice, regional medical care plans, veterans' medical care, the promotion of health, the prevention of disease, rehabilitation, training of physicians, health of the aging, rural health, military medicine, mental health, care of the chronically ill, medical research, industrial health, training of nurses, environmental health services, and training of auxiliary medical personnel.

During August and September, the Commission has planned to hold public hearings in several cities. All-day sessions are scheduled for Philadelphia, Houston, Detroit, San

Francisco and either Birmingham or Atlanta. If time permits other cities may be added. The Commission intends to invite representatives of major organizations in each area, such as medical societies and farm, labor and consumer groups. Individuals who care to testify will also be heard.

Although the Commission was severely criticized by the A.M.A. when it was created last December and again during the recent Annual Meeting in Chicago, it is nevertheless noteworthy that panel participation has included representation from the A.M.A. Board of Trustees and the top level of the many interested agencies and organizations. As reported prominently in the daily press at the time of the Chicago Convention, the House of Delegates agreed—though the vote was close—to withhold judgment of the Commission report until it has been published.

NEWS AND ANNOUNCEMENTS

The Western Institute on Epilepsy will hold its Fourth Annual Meeting in Los Angeles on Oct. 24 and 25. It will be particularly designed for the general practitioner and pediatrician, as well as for the public health officials and school personnel interested in the epileptic child and his school and home adjustments.

For further information write Dr. Jean P. Davis, College of Medicine, University of Utah, 168 Westminster Avenue, Salt Lake City, Utah, or Mrs. F. S. Markham, 1100 South Bay Front, Balboa Island, Calif.

* * *

The LeBonheur Children's Hospital, Memphis, Tenn., opened June 15, 1952. On June 14, 1952, members of the LeBonheur Club have invited members of the Memphis and Shelby County Medical Society and members of the Ninth District Dental Society to inspect the building and familiarize themselves with the facilities. On June 25 and 26, 1952, there was a Seminar sponsored jointly by the Medical Staff of the LeBonheur Hospital and the faculty of the Division of Pediatrics, University of Tennessee College of Medicine.

* * *

PRELIMINARY RESULTS REPORTED IN INTERNATIONAL STUDY OF RHEUMATIC FEVER TREATMENT WITH ACTH, CORTISONE OR ASPIRIN

Chicago: Scientific investigators of 3 nations who have been studying the comparative value of treating rheumatic fever with one of the hormones, ACTH or cortisone, or with aspirin have announced that although the acute symptoms of this disease usually subside with all 3 agents, no clear difference was as yet apparent in the rate of completeness of this improvement.

The report stated, "Although individual symptoms may appear to be affected more favorably by one or another of these drugs, no consistent pattern is evident which would allow any conclusion concerning the drug most effective for control of the acute illness."

It was pointed out that the results reported upon did not include any information on "the crucial question" of the comparative effectiveness of the 3 drugs in preventing chronic heart disease, which frequently follows rheumatic fever. The study will continue in an effort to arrive at an answer to this "important problem."

The cooperative rheumatic fever study, first of its kind in this field, is being conducted at 13 research centers in the United States, Great Britain and Canada. A central coordinating center is located in New York City. The preliminary report of its findings was presented at a joint scientific session of the American Heart Association's Council on Rheumatic Fever and the American Rheumatism Association on Saturday, June 7, at the Conrad Hilton Hotel in Chicago.

The report noted that the study had proved useful in contributing toward a clearer understanding of rheumatic fever. "For example," it was pointed out, "previous medical opinion indicated that the symptoms of rheumatic fever might vary in different countries whereas the patients being studied in the United States, England and Canada, are remarkably similar."

Since the study began in January, 1951, 658 patients have been admitted. The report was based on results in the first 302 of these cases.

The report was presented by a Panel of the investigators engaged in the study. The Moderator for the Panel was Dr. David D. Rutstein, Boston, Chairman of the Committee on Criteria and Standards of the Council on Rheumatic Fever. The Committee is conducting the study in conjunction with the British Medical Research Council.

The investigators cautioned that aspirin was not to be considered a "home remedy" for rheumatic fever, but had to be administered under careful medical supervision.

The study was originally undertaken as a long-range project, stimulated by early reports of the use of ACTH and cortisone. The cooperative study approach was adopted in order to obtain a large number of patients.

The investigators who participated in the Panel discussions included: Prof. A. Bradford Hill, statistician, and Dr. Eric G. L. Bywaters, representing the British investigating centers; Dr. Albert

Dorfman, La Rabida Jackson Park Sanitarium, Chicago; Dr. Edward E. Fischel, College of Physicians and Surgeons, Columbia University, New York; Dr. James E. Flett, Jr., Denver General Hospital, Denver; Dr. John D. Keith, Hospital for Sick Children, Toronto; Dr. Currier McEwen, New York University-Bellevue Medical Center, New York; Dr. Benedict F. Massell, House of the Good Samaritan, Boston; and Dr. Charles H. Rammelkamp, Francis E. Warren Air Force Base, Cheyenne, Wyo.

At each research center, a team of physicians, nurses, social workers, technicians and clerical help has been active in the study. The material collected, therefore, represents the efforts of literally hundreds of individuals in three countries.

Funds for the study are being supplied by the National Heart Institute of the U. S. Public Health Service, the British Medical Research Council, the hospitals and medical centers in the local communities involved in the study, the Armed Forces Epidemiological Board, the United States Air Force, the American Heart Association, and the Canadian Arthritis and Rheumatism Society. The supply of ACTH required for the study was given by Armour and Company, and the cortisone supply was given by Merck and Company.

BOOK REVIEWS

Clinical Pediatric Urology, Meredith Campbell, Philadelphia, W. B. Saunders Company, 1951, $18.00, 1113 pp.

In 1937 Dr. Campbell said in the preface to his two-volume *Pediatric Urology,* "Because there is no monograph today in any language which covers this broad field, the present volume aspires to this service." It filled the bill. The present *Clinical Pediatric Urology* represents an improvement and extension of this first edition, brought up to date and with many valuable additions.

The author has covered the field of pediatric urology in a most complete and exhaustive manner, making excellent use of his enormous material to acquaint the average urologist who does not have the opportunity to see a large pediatric material, and to acquaint the pediatrician and general practitioner with the many conditions that, if recognized early, may prevent irreparable kidney damage and the many unusual conditions, diseases, malformations, injuries, and tumors that occur in the urogenital tracts.

As in the first edition there is an excellent chapter on nephritis and allied diseases contributed by Goetsch and Lyttle. A separate chapter is also devoted to the adrenal gland and its relationship to the genital organs. The literature has been covered very extensively and an excellent bibliography is given at the end of each chapter. The chapter on urinary infection is particularly well done, from the point of view of the pediatrician. The book can be highly recommended as being in a class by itself in pediatric urology.

Diagnostik der Kinderkrankheiten, ed. 6, Prof. Dr. E. Feer, Vienna, Springer-Verlag OHG, 1951.

Emil Feer, pioneer-pediatrician of Switzerland, whose name is connected with the first monographic presentation of acrodynia, published this sixth edition of his *Diagnosis of Children's Diseases* at the age of 86 years. His capacity to combine historical knowledge with the evaluation of recent research reminds one of Abraham Jacobi and Isaac Abt.

Since the first edition (1921), the number of pages has increased from 275 to 461, the number of partly coloured illustrations from 226 to 285. In spite of all required corrections and additions, the original didactic principle of "semeiotic" presentation has been maintained. This teaching-method that disentangles the differential diagnosis without laboratory-aids from leading external signs such as physiognomy, cyanosis, sunken fontanel, turgor, etc., will always remain more important in the pediatric practice than in other specialties. Filatov (1847-1902) had titled his famous pediatric textbook "Semeiotics," and in the early days of Feer's pediatric career the presentation of symptoms still took the place of clinical analysis. In this new edition, however, it became necessary to compromise and to combine semeiotic teaching with adequate systematic consideration of modern clinical entities. Sections such as normal and abnormal growth, morphologic skull anomalies and skin diseases are amenable to semeiotic didactics, hence these parts of the new edition are excellent. But the principle had to be largely abandoned in the chapters on respiratory, cardiac, abdominal, blood and metabolic diseases. Feer's book gives special attention to those diseases that have been successfully studied during the last decade by his former co-worker and successor Fanconi (celiac disease, disturbances of the lipid metabolism). In the hematologic section, we find a combination of modern and obsolete concepts. This synthesis is stimulating from the historical point of view. For the younger student it is confusing that the traditional terms "proletarian anemia" and Jacksch's anemia have not yet been discarded in the sixth edition, though modern clinical entities like Mediterranean anemia, erythroblastosis, Fanconi's aplastic anemia are well described.

Most pictures are instructive for teachers and students. However, all attempts of textbooks to illustrate glandular enlargement, infectious arthritis and muscular hypertonia should be abandoned. All deviations that become apparent by movements should be demonstrated at the bedside or in films.